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# FOREWORD

GASTROENTEROLOGY embraces many different fields and interests. Indeed it may claim to be the core of general medicine and general surgery as these terms are understood today. Though no one can doubt that gastroenterology demands special application for the better understanding of its manifold problems, it is not in itself a specialty. It is an amalgam of many. In diagnosis, in treatment, and in investigation, it requires the cooperation of a team of workers, who will include at various times, and in different combinations, the clinician, whether physician or surgeon, the radiologist, the biochemist, the haematologist, the bacteriologist, the morbid anatomist, the nutrition expert, the physiologist, and the psychiatrist.

As a result of new and improved methods, the perfecting of surgical techniques, and field work into social problems, much headway has been made in the understanding and management of such conditions as dyspepsia not originating in ulcers, Crohn's disease, and ulcerative colitis, though the cause and treatment of peptic ulcer remain a major challenge. Much light has been shed on the physiology and histopathology of the liver and pancreas, and on the haemodynamics of portal hypertension; on the relation between blood groups and gastric disorders, and between alimentary disorders and the blood; on the metabolism of fats; on the motility of the oesophagus, and the mechanism of the cardia.

Malignant disease still casts its dark shadow, however, particularly in respect of cancer of the stomach, for which surgery alone can hope, at present, to bring relief. Despite signal advances of recent years in operative technique and some progress in diagnostic measures, the prospect for the sufferer remains bleak. Cancer of the mucus-secreting epithelium of the gastrointestinal tract presents such special difficulties to the cancer research worker that it is in danger of being neglected in favour of the more exciting and accommodating hormone-dependent growths, and the sarcomas, whose readier growth *in vitro* endear them to the laboratory worker.

It is to assist the further elucidation of these many and varied problems by providing a vehicle for the expression and interchange of ideas and for making easily and quickly available knowledge from all sources—bedside, laboratory, experiment—that this new journal, *Gut*, is dedicated. Its success depends upon the readiness of all who devote themselves to problems immediately or more remotely concerned with the study of gastroenterology to share their knowledge freely with their colleagues through the medium of its pages. It is hoped that the usefulness of the journal will not, however, be confined to those whose sole interest lies in one of the many different facets of gastroenterology, but to all medical men, whether they be in hospital or general practice, who are responsible for the welfare of patients.

HAROLD C. EDWARDS

[*Vandyk*

*Sir Arthur Hurst*

*Gut*, 1960, **1**, 3.

# HISTORY OF THE BRITISH SOCIETY OF GASTROENTEROLOGY

BY

THOMAS HUNT

The early history of the British Society of Gastroenterology is the history of Arthur Hurst. Son of a Bradford wool merchant, he was born in 1879 and died in 1944. He studied physiology at Oxford in 1899 and 1900 under Gotch and Haldane at the time when Sir Henry Acland, at the age of 85, had just been succeeded as Regius Professor of Physic by Sir John Burdon-Sanderson.

Hurst qualified from Guy's Hospital in 1905, and was elected to the staff of that hospital at the age of 27. Before this he travelled in Germany as Radcliffe Travelling Fellow of Oxford University and had worked both in Munich and (in 1906) in Boston and other cities in America.

The 64 years of his life covered a wonderful period of medical progress which began with the discovery of the tubercle bacillus by Robert Koch and ended with the first full use of penicillin in 1944. Hurst was at school, aged 16 years, when Röntgen discovered *x* rays (1895); he was 31 when Moynihan wrote his classic monograph on duodenal ulcer (1910); 45 when Elsner, Schindler, Henning, and others invented the gastroscope; and 59 when needle biopsy of the liver first showed the true nature of infective hepatitis (1939).

Hurst was born only 20 years after the publication of the *Origin of Species*, and the world of medicine in his early lifetime saw those advances in fundamental principles associated with the names of Pavlov, Ehrlich, James Mackenzie, Sherrington, and Thomas Lewis.

His earliest work began in 1906 when he was almost the first—if not the very first—man in England to use radiography for investigating the alimentary tract. His first subjects were students at Guy's Hospital to whom he was teaching physiology, and the reports of his findings on the act of swallowing a bismuth meal mark the beginning of that great step forward which barium meal examinations and all the later developments in gastroenterological radiology made in the diagnosis of digestive disorders.

This was at the time (1906) when gastric neurasthenia was much in vogue, and treatment by static electricity or by bitter tonics, such as the popular condurango, or by silver nitrate was especially favoured. Gastroenterology was almost wholly empirical and there was much discussion of such conditions as gastric myasthenia or atony of the stomach and ptosis of the viscera. Popular biliary stimulants were sarsaparilla and dandelion, and the strenuous Weir Mitchell treatment was in great use with isolation, rest, massage, forced feeding, and electrical stimulation of the skin from an induction coil; beef tea was the universal standby in diet.

Hurst's work with the bismuth meal led to knowledge of the movements of the alimentary tract and to recognition of the great variations in size and position in the abdomen of the stomach and colon in normal individuals. His paper on this subject published in the *British Medical Journal* (1907) is a landmark in gastroenterology, if only because it meant the end of much loose and speculative thinking on visceroptosis in general. This was followed by his book on constipation, and later, after his association with A. E. Barclay, by a series of investigations on the radiology of the digestive organs. Coincident with these advances in radiology what is now the great field of chemical pathology was also beginning. Though Hurst's interests were partly biochemical, his clinical activities spread to cardiology and neurology. With G. Goodhart he recorded the earliest case of auricular flutter after the discovery of the electrocardiograph by Sir Thomas Lewis in 1910, and as neurologist to Guy's Hospital he began to develop his interest in neurosis and hysteria. He was a fascinated attender in Paris at the clinics of Babinski and Dejerine and Pierre Marie. At about the same time (1908) he bought his first motor car, a two-cylinder Wolseley, which was the first consultant's car to penetrate into the courtyard of Guy's, hitherto sacred to the horse and carriage.

Hurst was a man who brought warmth and vitality into both his social and professional life, and always felt the importance of linking the two together in friendship and good fellowship. He was an original member of the Association of Physicians founded by Osler in 1907, and of the Medical Travelling Club

formed in 1927. When, as in cardiology, there arose the need for someone to bring together those working in this subject Sir James Mackenzie was there, so in gastroenterology was there Arthur Hurst. It was in 1936 that he first conceived the idea of forming a small gastroenterological club and asked one or two colleagues to dinner at the Athenaeum Club to discuss the project. In 1937 he proposed that a council of five be set up who would draft detailed plans for the club, and on November 19 and 20, 1937, the first meeting was held at the Royal Society of Medicine in London with Hurst as Chairman, the other members of Council being T. L. Hardy, T. C. Hunt, Sir Henry Tidy, and L. J. Witts. At this first meeting 36 members attended and there were seven visitors; the draft rules for the club were approved. The main subject discussed was gastroscopy, opened by Hartfall, followed by a discussion on alkalosis opened by Ryle and Dodds. At the dinner of the club held at the Langham Hotel (now an office building since suffering severe bomb damage in the war) Hurst gave his ideas and purpose in forming the club, the first rule of which was to read: "The objects shall be the advancement of gastroenterology and the promotion of friendship amongst those who have a special interest in disorders of the alimentary tract". Sir Robert Hutchison spoke of the desirability of admitting surgeons to membership. It is recorded in the minutes that "after discussion it was resolved that as the club numbered one radiologist (A. E. Barclay), one morbid anatomist (M. J. Stewart), and one biochemist (E. C. Dodds) of eminence, a surgeon occupying a similar standing should be elected, and it was unanimously agreed that Sir David Wilkie should be invited to occupy this position".

The second meeting of the club in 1938 was held at Cambridge with Sir John Ryle, who was then Regius Professor of Physic at the University, in the chair. Papers were read on many different subjects, and it was at this meeting that psychosomatic factors in ulcerative colitis, the action of aspirin on the gastric mucosa, and the biochemical changes in the blood after gastro-intestinal bleeding were first discussed. At this meeting T. L. Hardy was elected secretary. It is to him that a great part of the later success of the club is due, and his contribution to British gastroenterology is gratefully recognized by the Society which owes him so much.

An important decision, which Hurst himself regarded as a vital one, was also made at Cambridge, and it was to the effect that the club should choose for itself a new President every year, as opposed to electing a President who should hold office for three, five, 10 years, or longer. Since the first meeting in 1937 up to the present there have accordingly been 19 Presidents, the disparity being due to Hurst acting as unofficial chairman at two war-time meetings. Their names are as follows:—

| | |
|---|---|
| 1937 | Sir Arthur Hurst |
| 1938 | Sir John Ryle |
| 1940-42 | Sir Arthur Hurst (Chairman) |
| 1943 | Sir Henry Tidy |
| 1945 | Dr. Izod Bennett |
| 1946 | Sir H. Abrahams |
| 1947 | Sir Ernest Spriggs |
| 1948 | Prof. T. L. Hardy |
| 1949 | Dr. Geoffrey Evans |
| 1950 | Sir John McNee |
| 1951 | Prof. W. MacAdam |
| 1952 | Dr. A. H. Douthwaite |
| 1953 | Sir Stanley Davidson |
| 1954 | Dr. S. Patterson |
| 1955 | Prof. L. J. Witts |
| 1956 | Dr. T. C. Hunt |
| 1957 | Prof. C. F. Illingworth |
| 1958 | Sir Charles Dodds |
| 1959 | Prof. H. Rodgers |
| 1960 | Mr. Harold Edwards |

During the 1939-45 war two meetings were held, one at Oxford in 1941 when the subject of dyspepsia in members of the Forces was discussed, and one in London when it was suggested that the club might exert its authority in the form of some published statement on the prevention of peptic ulcer recurrences. This arose from Hurst's criticism of his own methods for ulcer prevention. Discussion soon made it clear that the club was in no position to issue any agreed advice, and as Hardy recorded: "Although there was no agreement on either fundamentals or details, there was abundant evidence of a healthy individualism and a dislike for any sort of authoritarian régime." The meeting arranged for May 10, 1940, was cancelled owing to the invasion of Holland, but a few members dined together as guests of Hurst at the Athenaeum.

On August 17, 1944, Hurst died suddenly in Hardy's house at Birmingham, and no meeting of the club was held that year. Hurst's spirit and vitality had stood up well to the period of war strain when he had returned to work at the Oxford he loved, and in spite of asthma and the deafness which had taxed him for many years he was full of energy and his own enthusiasm to the end of his life. Though some of his many original ideas proved wrong, his brilliant work on achalasia of the cardia, on dyschezia, and on chronic gastritis as a precursor of gastric cancer, are only three examples of his far-sighted conceptions which have been confirmed by the passage of time. His role as a stimulator of medical thought, and as a promoter of international cooperation, research, and friendship is not less important than his achievements in the advancement of knowledge.

In 1945 the club which he had founded recorded the following resolution:

> "That the Club records its deep regret at the death of its founder the first Chairman, Sir Arthur Hurst, and desires to place on record its great appreciation of his services to the Club, his many original contributions to gastro-enterology and his outstanding qualities as a physician and teacher."

After Hurst's death the small club of 40 original members decided to change its title to that of the "British Society of Gastro-Enterologists" and the existing rules were slightly changed; in 1949 the present title of "British Society of Gastroenterology" was adopted. During the 15 years of its existence the Society has grown in strength and prestige. Dr. Hunt, Mr. Hermon Taylor, and Dr. W. Bourne have successively followed Dr. Hardy as secretaries. *Gastro-Enterologia* has published the proceedings of the meetings which have been held yearly in November. In 1948, a proposal to establish a British *Journal of Gastroenterology* was studied by a small committee. It was then thought that there were not more good gastroenterological papers than could be satisfactorily—if not better—published in general medical journals than in a specialized journal which might only be read by a limited number of doctors. The proposal was accordingly decisively outvoted at the Society's meeting, and it was not until 10 years later that it was again brought forward.

During these 10 years a number of notable happenings took place both in the life of the Society and in gastroenterology in general. In the first place the Society began again to take an active part in international meetings. It had been agreed in Paris in 1937 to hold the third International Congress of Gastro-Enterology in London in 1940 with Sir Arthur Hurst as President and Dr. Hunt as secretary. This meeting was of course cancelled and it was not until 1952, when truly international meetings again became possible after the war, that the British Society was officially represented at the meeting of the Association of the National European and Mediterranean Societies of Gastro-Enterology at Bologna. In July, 1956, the British Society acted as host in London at the fifth meeting of this Association. It was attended by over 800 visitors and delegates, including many distinguished physicians, surgeons, and others from North America and other parts of the world. It was generally agreed that this meeting reached a high standard and both the scientific and social programmes were carried through with great success.

The proceedings of this Congress were splendidly edited by Harold Edwards and published by Messrs. Karger within a few months of the end of the meeting. The 800-page volume which emerged is undoubtedly an important addition to gastro-enterological literature. Since the London meeting, the World Organization of Gastro-Enterology has been founded and has held its first meeting in Washington, U.S.A., in 1958, under the brilliant Presidency of Dr. H. Bockus. The British Society gives its strongest support to this Association, as it does to the Association of European Societies, and hopes to play an increasingly active rôle in the field of international research and postgraduate education.

In addition to these developments in European and world meetings, the Society's own meetings have brought forward an increasing number of new contributions to knowledge, and there has been a rapidly mounting number of younger British physicians, surgeons, and research workers specializing in gastroenterology.

The volume of new papers, both scientific and clinical, is shown by some examples of the subjects discussed at the Society's meetings.

1948, Birmingham, disorders of the small intestine
1949, London, gastric acid secretion
1950, London, post-gastrectomy syndrome
1951, Leeds, hiatus hernia
1952, London, haemopoiesis in relation to disorders of the alimentary tract
1955, Edinburgh, abdominal visceral blood flow
1956, Oxford, carcinoid tumours; anticholinergic drugs; the secretion of mucus, etc.
1958, London, blood groups
1959, Belfast, hormones and the alimentary tract

At the Society's meetings many short papers are read and in most cases there are demonstrations and medical exhibitions so that new contributions have grown steadily in number and sometimes in complexity. At the same time more visitors interested in gastroenterology have attended, and in 1939 the number of members elected was increased from 65 to over 100.

And so, in 1960, the time has come for a journal, a time when both the special interests of gastroenterology, and the size and authority of the British Society of Gastroenterology have justified it. British medicine has a mistrust of narrow specialization and holds that just as a specialist must not lose touch with the main strain of medicine or surgery, so a specialist journal must be born out of the development of general medicine and must retain its contact with it; it must be a necessity fulfilled because the specialty needs it as an essential development of an advancing subject. Such, I believe, is *Gut*. As the Journal of the British Society of Gastroenterology it has an established parentage and background, and a future that, I am confident, will add distinction to gastroenterology.

*Gut*, 1960, **1**, 6.

# EARLY INVESTIGATIONS OF HAEMATEMESIS*

BY

G. N. CHANDLER, A. D. CAMERON, A. H. NUNN, and D. F. STREET

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Most series of haematemesis or melaena present data about the clinical problems in relation to the final diagnosis. When a patient is admitted there is the problem of management which depends to a considerable extent on the diagnosis. This paper demonstrates that it is possible to achieve an accurate diagnosis in 80% during the first 24 hours.

"This, which we have seen as the result of ulceration, also occurs without any such disease; and I have seen it fatal where no organic disease could be discovered, and even the source of the haemorrhage could not be detected."

This reference to haematemesis appeared in a treatise, published in 1830, by Abercrombie, first Physician to the King in Scotland. Well over a century later, and despite advancing knowledge in the fields of diagnosis and pathology, there is still considerable difficulty experienced during the acute stages of haemorrhage in identifying the cause of bleeding. In the extensive writings on the causes and proper management of haematemesis the initial diagnostic problems only too often become submerged in comfortable tables of final diagnosis.

Peptic ulcer is undoubtedly the most important cause of the admission of patients for haematemesis and melaena. In Avery Jones' series (1956) of 1,910 admissions for this emergency, 1,764 were due to proved or probable peptic ulcer. Fraenkel and Truelove (1956) reviewed 845 patients admitted to hospital with haematemesis. Seven out of every 10 showed convincing evidence of a chronic peptic ulcer; acute ulcers accounted for haematemesis in a further one in every six patients. The other single causes, in both series, which contributed appreciable numbers were oesophageal varices and carcinoma of the stomach. Though in most patients with chronic ulcers radiological or operative confirmation is obtained, this is rarely so in the case of bleeding acute ulcers. Thus Needham and McConachie (1950) could give only an approximate estimate of the proportion of their patients with haematemesis who had bled from acute peptic ulcer. Avery Jones (1956) and Tanner (1954) achieved greater diagnostic accuracy by early gastroscopy combined with surgery and radiology, judging between 6·5% and 29·3% of patients to have bled from acute ulcers. In most series the diagnosis rests upon negative radiological findings, and Avery Jones (1956) commented that a greater proportion of this radiologically negative group would probably be found to have an acute gastric lesion if gastroscopy were done soon after admission.

Acute peptic ulceration is a common lesion which normally responds well to medical treatment, but a firm distinction between acute and chronic ulcer is impossible on clinical grounds alone. Yet with mounting recognition of the rôle of surgery in the treatment of bleeding chronic peptic ulcer and of the good prognosis of the bleeding acute lesion with medical management, the inadequacy of present diagnostic methods assumes increasing importance. Optimal conditions for successful surgery demand an early decision in suitable patients, and the early diagnosis of the cause of haematemesis is an important factor in the successful management of the individual patient.

Three procedures are available to the clinician which, if applied in the acute stages of illness, can yield diagnostic information. These are gastric aspiration, gastroscopy, and early examination by barium meal. This communication attempts to assess the value of these three investigations as a combined procedure for the early diagnosis of the cause of bleeding.

## Gastric Aspiration

Kaufmann (1910) and Hurst (1924) recommended gastric lavage in the acute stages of haematemesis, to empty the distended stomach and thereby to secure its contraction and arrest haemorrhage. Wangensteen (1940), Kinsella (1950), and Lewis (1950) also reported favourably on the value of gastric aspiration in haematemesis. Chandler and

* Presented at the meeting of the British Society of Gastroenterology at Belfast on November 6, 1959.

Watkinson (1953, 1958, 1959) considered that early gastric aspiration yielded valuable information; the observation at the bed side of blood staining in the aspirated specimens was useful because further haemorrhage could be detected before other clinical criteria had indicated its presence, and the association of clear gastric specimens with evidence of continued blood loss indicated that the site of haemorrhage was beyond the pylorus. By studying the acidity of aspirated specimens they showed that high nocturnal acidity is usual in bleeding chronic ulcer, that nocturnal neutralization is commoner in bleeding than in uncomplicated gastric ulcer, and that achlorhydria is observed at the time of haemorrhage in acute peptic ulceration. On this basis the site and type of ulcer responsible for gastrointestinal bleeding was accurately predicted in a significant proportion of the patients investigated.

### Gastroscopy

Gastroscopic examination is a feasible undertaking in most patients admitted to hospital because of unexplained bleeding from the upper gastrointestinal tract. It should be done as soon as possible after admission, particularly if it is to aid in the detection of acute peptic ulcers and gastric erosions which heal rapidly without trace. If the lesion responsible for bleeding lies in the stomach it can usually be demonstrated, and whenever possible the flexible Hermon Taylor gastroscope, which gives a better view of the stomach and particularly of the posterior wall, should be used. In women over 50 the Wolf-Schindler gastroscope is the safer instrument. Heart failure, thoracic and cervical spinal deformity, and serious lung disease contraindicate the examination, which is performed at the Central Middlesex Hospital after premedication with "nembutal" and "omnopon" and scopolamine. It is sometimes difficult to predict these requirements accurately, and excellent premedication can often be obtained by reducing or omitting the dose of barbiturate and giving pethidine, 50-100 mg. intravenously, at the time of gastroscopy, should anxiety, restlessness, or a prominent gag reflex indicate its use.

Occasionally, by insufflation of air into the gullet during withdrawal of the gastroscope, oesophageal varices may be seen and at times a hiatus hernia can be diagnosed. However, if a lesion is suspected in the lower oesophagus, oesophagoscopy is a more certain method of obtaining information.

### Early Barium Meal Examination

Early barium meal examination has been adopted in some centres as a means of obtaining diagnostic information, and the technique elaborated by Hampton (1937) and followed by Schatzki (1946) is considered safe by many observers. The procedure has been criticised on the grounds that any manipulation of the patient carries the risk of initiating further haemorrhage. Cantwell (1959) has shown that useful information can be obtained by modified examination of the patient in his bed using a portable *x*-ray apparatus and avoiding manipulation.

At the Central Middlesex Hospital early radiological investigation of haematemesis is done on the ward with a portable *x*-ray machine. No screen control is used and no palpation of the abdomen is necessary. Four ounces of barium suspension are drunk as rapidly as possible by the patient who is then turned into the right lateral position with the film cassette and grid beneath him. An exposure is made in this position, followed in quick succession by right anterior oblique, right posterior oblique, and antero-posterior projections. The technique of early radiological investigation of bleeding from the upper gastrointestinal tract has been described by Street, Nunn, Cameron, and Chandler (1960).

### Combined Investigation

It has been our experience that correct early diagnosis of the cause of haematemesis and melaena is best achieved by a combination of gastric aspiration, gastroscopy, and barium meal examination in the ward. The following procedure has been adopted (Table I):

Table I

PROCEDURE FOR EARLY INVESTIGATION OF HAEMATEMESIS

| Day | Time | Method | Technique |
|---|---|---|---|
| First | Admission | Hourly gastric aspiration | *p*H analysis |
| Second | 9.00 a.m. | Gastroscopy | Hermon Taylor gastroscope, local anaesthesia |
| Second | 2.00 p.m. | Ward barium meal | 4 oz. barium. Films, right lateral, right anterior oblique, right posterior oblique, supine |

As soon as the patient has been made comfortable after admission to the ward, a Ryle's tube is passed via the nose and secured to the cheek with adhesive strapping. About 5 ml. of gastric contents is aspirated hourly by syringe suction and the samples kept in numbered and stoppered bottles. The *p*H of the specimens is estimated electrometrically at the end of the intubation period which finishes at 9 a.m. on the day after admission, when the last specimen is obtained. The stomach is then emptied through the indwelling tube and gastroscopy performed. Later that morning or in the early afternoon of the same day, barium meal examination is made on the ward using the portable *x*-ray apparatus and the technique described above.

The usual requirements of resuscitation are met by generous blood transfusion, and the accepted régime of early feeding and rehydration is followed without serious encroachment by these diagnostic precedures. It is necessary to withhold food and fluids only for two hours preceding radiological examination. Intravenous therapy, where indicated, continues undisturbed. In about two-thirds of admissions for haematemesis all three investigations have been completed and no ill effects have been observed.

### Analysis of Clinical Cases

One hundred and two patients, admitted urgently with haematemesis or melaena or both to the Gastroenterological Unit at the Central Middlesex Hospital, were studied by the combined procedure of gastric aspiration followed by gastroscopy and barium meal examination in the ward. They represented consecutive and unselected admissions for gastroduodenal bleeding over the period October, 1958, to May, 1959. The final diagnosis in each case was made at necropsy, at operation, or at a second barium meal examination done in the *X*-ray Department. The assumed cause of bleeding, and the criteria employed in final diagnosis (which must necessarily be made independently of the early diagnostic procedures), are summarized in Table II.

Of the 102 patients studied, 18 were finally assigned to the group of chronic gastric ulcer, 38 had bled from chronic duodenal ulcers, and 41 from acute lesions. There were two admissions for haemorrhage from carcinoma of the stomach in this series and three patients had bled from oesophageal varices consequent on portal hypertension. Verification of the cause of bleeding was obtained at operation in 15 cases, at necropsy in three, and in the remainder at a second barium meal examination done in the *X*-ray Department after haemorrhage had stopped.

TABLE II
PATIENTS INVESTIGATED

| Diagnosis | Number of Cases | Diagnostic Criteria | | |
|---|---|---|---|---|
| | | Operation | Final Barium Meal | Necropsy |
| Chronic gastric ulcer | 18 | 5 | 13 | — |
| Chronic duodenal ulcer | 38 | 6 | 32 | — |
| Acute lesion group | 41 | 3 | 36 | 2 |
| Carcinoma of stomach | 2 | 1 | — | 1 |
| Portal hypertension | 3 | — | 3 | — |
| Total | 102 | 15 | 84 | 3 |

### Results of Early Investigation

Of the 97 patients in the series who had bled from peptic ulcer, either acute or chronic, 58 were studied by all three procedures during the initial stage of their illness; in 25 only two tests were possible and in 14 only one investigation was performed. In roughly two-thirds of admissions for haematemesis, therefore, all three were possible and no ill effects were observed nor was the mortality adversely affected.

Table III summarizes the results obtained by the early application of the three diagnostic procedures during the acute stage of bleeding in the 97 patients of the peptic ulcer group.

Secretory studies—estimations of intragastric *p*H during or immediately after bleeding—were carried out in 76 patients. Secretion patterns which accurately predicted final diagnosis were obtained

TABLE III
ACCURACY OF PREDICTION OF FINAL DIAGNOSIS BY THREE METHODS OF INVESTIGATION IN PEPTIC ULCER GROUP

| Final Diagnosis | No. of Cases | No. Studied | Diagnostic | Not Diagnostic | Lesion Seen | Lesion Not Seen | % Accuracy |
|---|---|---|---|---|---|---|---|
| *Secretion Patterns* | | | | | | | |
| Chronic gastric ulcer | 18 | 14 | 7 | 7 | — | — | 50 |
| Chronic duodenal ulcer | 38 | 32 | 21 | 11 | — | — | 66 |
| Acute lesion group | 41 | 30 | 18 | 12 | — | — | 60 |
| Total | 97 | 76 | 46 | 30 | — | — | 60 |
| *Gastroscopy* | | | | | | | |
| Chronic gastric ulcer | 18 | 12 | — | — | 9 | 3 | 75 |
| Chronic duodenal ulcer | 38 | 25 | — | — | 0* | 18 | — |
| Acute lesion group | 41 | 33 | — | — | 18** | 15 | 55 |
| Total | 97 | 70 | — | — | 27 | — | — |
| *Early Barium Meal* | | | | | | | |
| Chronic gastric ulcer | 18 | 15 | — | — | 9 | 6 (0 incorrect) | 60 |
| Chronic duodenal ulcer | 38 | 37 | — | — | 27 | 10 (0 incorrect) | 73 |
| Acute lesion group | 41 | 40 | — | — | — | 35 (5 incorrect) | 87 |
| Total | 97 | 92 | — | — | 36 | | 77 |

* Seven patients showed mammillation: ** 13 patients had acute ulcers, five patients showed acute superficial gastritis

in 50% of patients bleeding from chronic gastric ulcer (based on nocturnal neutralization), in 66% of chronic duodenal ulcer subjects (based on high night acidity), and in 60% of acute ulcer patients (based on achlorhydria).

Gastroscopic examination was performed in 70 patients, and, as might be anticipated, proved most useful in the recognition of chronic gastric ulcer, the lesion responsible for bleeding being seen in three-quarters of cases. In bleeding duodenal ulcer, gastroscopy plays an important negative rôle in diagnosis, serving mainly to exclude a gastric lesion, though in seven patients the presence of a chronic duodenal lesion was suspected from the abnormally rugose appearance of the mucosa. Mucosal abnormalities were evident at gastroscopy in 18 of 33 patients (55%) assumed to have bled from acute lesions, 13 patients showing discrete acute ulcers and five a diffuse acute superficial gastritis.

Radiological examination in the ward was done in 92 patients. A confident diagnosis of chronic gastric ulcer was made in nine of 15 (60%) patients bleeding from this cause. More valuable was the ability of this bedside investigation to diagnose chronic duodenal ulcer in 27 of 37 patients (73%), and 35 of 40 patients (87%) were correctly labelled as bleeding from acute lesions on the basis of normal radiological findings.

The histogram (Fig. 1) shows the pre-eminence

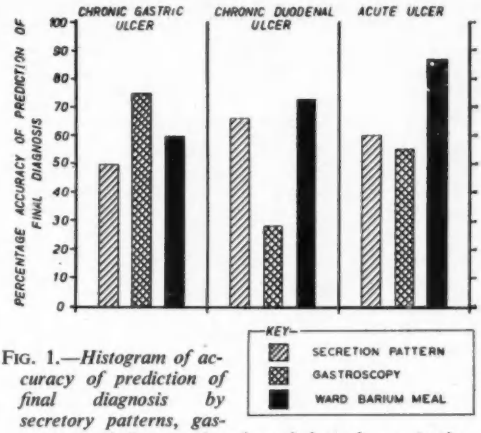


FIG. 1.—*Histogram of accuracy of prediction of final diagnosis by secretory patterns, gastroscopic findings, and early radiological examination.*

of early *x*-ray examination in forecasting the correct diagnosis amongst acute ulcer patients and those with chronic duodenal lesions. Gastroscopy proved to be the most valuable diagnostic aid in the recognition of chronic gastric ulcer.

It should be noted, however, that this method of presenting data undervalues the rôle of gastroscopy, an examination which cannot provide direct evidence of chronic duodenal ulcer. However, the finding

TABLE IV

CORRELATION OF SECRETORY, GASTROSCOPIC, AND EARLY RADIOLOGICAL DIAGNOSES WITH FINAL DIAGNOSIS OF CAUSE OF BLEEDING

| | | Gastroscopic Findings | | | |
|---|---|---|---|---|---|
| | | Acute Ulcer | Nothing Abnormal Discovered | Gastric Ulcer | Not Done |
| *Secretory Diagnosis of Acute Ulcer in 27 Patients* | | | | | |
| Radiological Diagnosis | Nothing abnormal discovered | 8 | 7 | 1 | 2 |
| | Gastric ulcer | — | 2 | 1 | 1 |
| | Duodenal ulcer | — | 2 | — | 2 |
| | Other | — | 1 | — | — |
| | | Radiological Findings | | | |
| | | Gastric Ulcer | Duodenal Ulcer | Nothing Abnormal Discovered | Not Done |
| *Gastroscopic Diagnosis of Gastric Ulcer in nine Patients* | | | | | |
| Secretory Diagnosis | Gastric ulcer | 2 | — | 1 | — |
| | Duodenal ulcer | 1* | — | — | — |
| | Acute ulcer | 1 | — | 1 | — |
| | Not done | 1 | — | 1 | 1 |
| | | Gastroscopic Findings | | | |
| | | Nothing Abnormal or Mammillation | Gastric Ulcer | Not Done | |
| *Radiological Diagnosis of Duodenal Ulcer in 27 Patients* | | | | | |
| Secretory Diagnosis | Duodenal ulcer | 11 | 1* | 4 | |
| | Gastric ulcer | 1 | — | — | |
| | Acute ulcer | 2 | — | 2 | |
| | Not diagnostic | 3 | — | — | |
| | Not done | 1 | — | 2 | |

* Combined ulcers

of mammillation suggests this cause, and the presence of atrophic gastritis is of great help in excluding it. At the clinical level, negative information from gastroscopy has great value in the diagnosis of the cause of bleeding.

Of greater importance than the comparative merits of these three diagnostic procedures in haematemesis is the degree to which the information derived from them can be correlated. The greater the area of agreement between tests, the more confident can the clinician be in making a diagnosis of the site and type of lesion responsible for bleeding.

Table IV shows the mutual relationship of information obtained from the tests.

When the secretory diagnosis was acute ulcer, supporting evidence was obtained from radiology and gastroscopy in 15 of 22 patients in whom all three tests were made. The number of patients in the gastroscopic gastric ulcer group is too few for useful comment, but the third table shows that, given a radiological diagnosis of duodenal ulcer, unanimity was achieved in 11 out of 18 instances where all three investigations were done.

Agreement in two or more tests was much greater, as is shown in Table V.

TABLE V

EXTENT OF AGREEMENT IN TWO OR MORE TESTS IN 83 PATIENTS (PEPTIC ULCER GROUP)

| Final Diagnosis | No. of Patients | Gastroscopy-positive Cases | Including Gastroscopy-negative Cases |
|---|---|---|---|
| Acute ulcer | 35 | Agree in 3: 8/27<br>Agree in 2: 26/35 | 13/27<br>35/35 |
| Duodenal ulcer | 33 | Agree in 3: 3/23<br>Agree in 2: 18/23 | 11/23<br>25/33 |
| Gastric ulcers | 15 | Agree in 3: 2/8<br>Agree in 2: 7/15 | |

If allowance be made for negative findings at gastroscopy as being of value in the diagnosis of the cause of bleeding, it will be seen that agreement in two or more tests was complete in all patients bleeding from acute ulcers. In chronic duodenal ulcer agreement in two or more tests was reached in 25 of 33 patients. With patients bleeding from chronic gastric ulcer, gastroscopy must give positive information to be of value, and in this group agreement between two or more tests was obtained in only seven of 15 cases. But in a further three of these 15 patients gastroscopy had shown a chronic ulcer in the stomach, and in another patient an unequivocal ulcer niche was demonstrated by early *x*-ray examination.

In 20 patients the results of early investigation were either contradictory or insufficiently precise to enable a confident assumption of the cause of bleeding to be made. In the remaining 77 patients (80%) of the ulcer group, correct early diagnosis was achieved on the basis of the combined investigations, usually within 24 or 36 hours from admission. Table VI compares the clinical diagnosis on admission, based on the history of illness and the results of previous investigation, with the diagnosis reached by combined early investigation.

TABLE VI

CLINICAL IMPRESSION OF CAUSE OF HAEMORRHAGE COMPARED WITH DIAGNOSIS FROM EARLY INVESTIGATION IN PEPTIC ULCER GROUP

| Final Diagnosis | No. of Patients | Correct Diagnosis on Admission (%) | Correct Diagnosis from Early Investigation (%) |
|---|---|---|---|
| Acute ulcer | 41 | 37 | 85 |
| Duodenal ulcer | 38 | 55 | 79 |
| Gastric ulcer | 18 | 17 | 66 |
| Total | 97 | 42 | 80 |

The greater reliability of the early diagnostic procedures in forecasting correct eventual diagnosis is well shown in each of the three groups of chronic gastric ulcer, chronic duodenal ulcer, and acute ulcer.

The results obtained by early investigation of the cause of bleeding after haematemesis have provided clear evidence of its value, not only in the facilitation of earlier diagnosis but notably also in the management of patients who bleed again after admission to hospital. In the present investigation 15 patients underwent partial gastrectomy, in nine of whom operation was done as an emergency procedure for uncontrolled bleeding. Emergency gastrectomy was necessary in two patients bleeding from chronic duodenal ulcer and in both a firm pre-operative diagnosis of the cause had been made. Three of four emergency gastrectomies in the group of patients bleeding from chronic gastric ulcer were undertaken with foreknowledge of the responsible lesion. Severe recurrent haemorrhage may demand operation even though a pre-operative diagnosis of acute peptic ulceration has been made by early investigation, as in two of three patients in whom surgery was required (with one post-operative death from pulmonary embolism).

Nevertheless, despite careful investigation and as complete assessment of the patient as was possible within the framework of this study, mistakes occurred, as the following case illustrates.

CASE REPORT.—A man of 46 gave a 20-year history of upper abdominal discomfort occurring one hour after food with long periods of relief. Fifteen years ago he had had an attack of melaena. He was admitted to the Central Middlesex Hospital after a further attack of melaena. Immediate intubation showed extremely high levels of gastric acidity at night, no lesion was seen in

FIG. 2

FIG. 3

FIG. 4

FIG. 2.—*Film taken in the ward of barium meal examination of a man aged 36 admitted after haematemesis. Note moderate-sized benign gastric ulcer.*

FIG. 3.—*Barium meal film taken in the ward of a man aged 52 admitted with haematemesis and melaena. Note deformed duodenal cap containing an ulcer crater.*

FIG. 4.—*Barium meal film taken in the ward of a man aged 68 admitted because of recent haematemesis. Note narrowing of proximal stomach and infiltration of lower oesophagus by carcinoma.*

the stomach at gastroscopy the next morning, and barium meal examination in the ward disclosed the presence of a duodenal ulcer. This lesion was confirmed at a subsequent barium meal examination in the *X*-ray Department which showed no other abnormality. Blood group was 0 + ve. He made a good recovery, aided by blood transfusion, and was discharged home after 11 days. Because of recurrent pain, operation was advised when he was next seen in the Out-patient Department, but was declined by the patient. Two months later he was readmitted with the signs of ascites and an obviously malignant infiltration of the liver from a primary growth in the fundus of the stomach.

However, the small amount of misleading information is notable, particularly from gastroscopy and radiological examination in the ward, incorrect assumptions being made in only five cases out of 92 patients studied by early radiography. Figs. 2, 3, and 4 are photographs of *x*-ray films taken with the portable *x*-ray apparatus and demonstrate the value of this method in early aetiological diagnosis.

Inevitably some patients escaped inclusion in this investigation during the period of study. These exclusions mainly concerned the old and frail, those acutely ill from haemorrhage whose only hope lay in immediate surgery, and finally, a group of patients whose illness was either too mild to justify immediate investigation or in whom associated diseases contraindicated it. Three patients were not investigated because of their general enfeeblement. One of these, a diabetic woman aged 84, died from bed sores and further bleeding three weeks after admission, and necropsy showed acute gastric ulcers. Two patients died a few hours after admission; a woman aged 65 succumbed to exsanguinating haemorrhage from a large artery in the base of a chronic gastric ulcer shortly after entry to the ward, and a man aged 61, whose duodenal ulcer had both perforated and bled, died on the second hospital day from peritonitis. Four patients admitted with haematemesis or melaena were not studied because of severe associated diseases; congestive heart failure and cor pulmonale most commonly prohibited early investigation. There were no deaths in this group. Thirteen patients, admitted after gastro-duodenal haemorrhage were not investigated for reasons that lay outside our control. None of these patients died.

We are not primarily concerned in this communication with the effect of early investigation and subsequent treatment on mortality from bleeding peptic ulcer. The numbers are too small to form an important basis for comparison with other series or previous experience. There were two deaths amongst 97 ulcer patients studied by immediate investigation, and in the whole period under review, of 119 patients admitted because of haemorrhage from peptic ulcer, five died, a mortality rate of 4·2%. Nevertheless these figures indicate that the

procedure of early investigation is safe, and suggests that its application may well be effective in lowering mortality.

## Discussion

The difficulty in correctly diagnosing the cause of the haemorrhage has been recognized in previous reports dealing with haematemesis, especially in the acute stages. A short history of preceding dyspepsia is more commonly found in those patients bleeding from acute than from chronic peptic ulcers, but the diagnosis is not always obvious and the history often misleading. The circumstances of a shocked patient, anxious relatives, and the pressing demands of resuscitation only too often militate against accurate history taking. We have frequently been impressed by the relative ease with which peptic ulcer can be diagnosed in the ambulant patient attending the Out-patient Department compared with the difficulties surrounding the same conclusion in the emergency ward after an attack of haematemesis. Yet early accurate identification of the lesion responsible for bleeding is essential if the mortality from haematemesis is to be reduced from its present unsatisfactory level. By no means easy, the problem must be solved of detecting those patients in whom the prognosis with medical treatment must be considered poor, and who will bleed to death unless surgery is employed. If chronic peptic ulceration can be diagnosed with reasonable confidence, operative treatment is to be recommended for those older patients in whom bleeding is severe or recurs after admission to hospital. As early as 1918 Finsterer (1939) proposed the application of radical surgical measures, the operation being performed within the first 24 to 48 hours from the onset of haemorrhage; his reported operative mortality for early cases was 5%. Gordon-Taylor (1935) commented:

> "Finsterer's first 48 hours is still the optimum period for surgical attack in haematemesis and the golden age of gastric surgery will have been attained only when all cases of haemorrhage from chronic ulcer come to operation within that space of time."

And Tanner (1954) found that the best results were obtained by early and frequent surgery. While the mortality with medical management can be as low as that achieved by Meulengracht (1935), it is unlikely that a universal surgical approach will provide comparable success and achieve wide popularity. In general, surgical intervention has been limited to selected patients (Bohn, 1949; Parsons and Aldridge, 1951; Pedersen, 1951), the best results being achieved by prompt surgery in patients with proved or probable peptic ulcers. As Tanner (1950) has stressed, the criterion for success or failure of a surgical policy is its influence on overall mortality and not the mortality for surgical intervention as such, which depends on the type of risk accepted. Avery Jones (1947), in a study of 400 consecutive admissions for haematemesis, found particular indications for emergency gastrectomy in patients over 50 years with good clinical evidence of chronic peptic ulcer who had brisk recurrent haemorrhage after admission. The same author (1952) again showed that in the group of middle-aged or older subjects with chronic peptic ulceration the mortality is high with medical treatment, and that it is in such patients that the best surgical contribution to the reduction of mortality can be achieved, provided an early decision is made in suitable cases.

Decisions as to correct treatment of the patient with haematemesis most often depend on clinical judgment and there is need for a method of investigation that will yield reliable diagnostic information in the acute stages of illness. The results obtained in this investigation by combining gastric aspiration with gastroscopy and barium meal examination in the ward have provided good evidence of its usefulness in the facilitation of earlier diagnosis of the cause of bleeding. Thus correct early diagnosis was achieved by means of combined investigation in 80% of patients with haemorrhage from peptic ulcer, usually within 24 or 36 hours from admission. These early diagnostic procedures proved to be much more reliable in forecasting the correct diagnosis than did the clinical impression of the cause of bleeding. From knowledge of the results obtained by early investigation a more confident assumption could be made as to the pathological basis of the illness than would otherwise have been possible.

The experience gained from this investigation has an important practical application in the management of haematemesis. Thus, when the early diagnostic procedures indicate the presence of chronic peptic ulcer, and if bleeding occurs after admission, the surgeon on duty is asked to see the patient, especially if over 45 years of age, with a view to immediate operation. If bleeding has stopped, surgery is delayed pending further evidence of recurrence. Chronic gastric ulcer is a particular indication for surgery; bleeding from this source carries a high mortality under medical treatment and its operative arrest by gastrectomy is generally easier than is the surgery of chronic duodenal ulcer. When the evidence from early combined investigation indicates that haemorrhage is from acute peptic ulcer, continued medical treatment is generally advisable. Nevertheless surgery may still be required to control bleeding in such patients; continued massive haemorrhage is an indication for

surgical intervention, though the need for this is rarely so urgent as in bleeding chronic peptic ulcer. In every patient all evidence of chronic peptic ulcer from previous investigations must be given due regard, in conjunction with the history before admission, in order to assist the final decision between operative and conservative treatment.

The importance of reaching an early decision as to the surgical treatment of haematemesis cannot be overemphasized. Rapid deterioration, in circumstances of recurrent bleeding despite apparently adequate replacement of blood by transfusion, is common, and delay in seeking surgical aid often fatal. Every patient with haematemesis presents a new challenge to diagnosis and proper management. When the physician is guided by all the facts available from the history, examination, and investigation, correct appraisal is greatly facilitated. Confidence in the recovery of such patients, under either medical or surgical treatment, is usually justified by the event.

The adoption of a policy whereby early diagnosis of the cause of bleeding can be achieved has been found to confer other benefits, particularly in respect of the length of stay of the patient in hospital. Most patients admitted after gastro-duodenal haemorrhage do not bleed again, but despite this it is usual for rest in bed to be enforced until they are judged to be fit for barium meal examination in the *X*-ray Department, after which slow convalescence is allowed. If the procedure of early investigation is followed, there is no reason why the patient whose recovery is uncomplicated should be retained in hospital for this purpose; a second barium meal examination is unnecessary except in the small number of cases where the results of early investigation are conflicting. In the majority of patients barium meal examination in the ward can be accepted as a satisfactory alternative to later radiological investigation. There is no evidence to suggest that recovery after haematemesis is hastened by confinement to bed, the dangers of which are obvious, especially in older subjects with associated degenerative disease. There is little doubt that, fortified by a diagnosis of the cause of bleeding reached in the acute stages of illness, and in the presence of satisfactory clinical progress, the physician can best serve the interests of the patient by allowing early ambulation. The saving in the time a bed is occupied that results is considerable, and the advantages of this policy are shared equally by the patient, who enjoys an earlier return to his home, and the physician, whose waiting list is materially influenced to the benefit of other patients awaiting admission.

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# THE INCIDENCE OF CHRONIC PEPTIC ULCER FOUND AT NECROPSY

## A STUDY OF 20,000 EXAMINATIONS PERFORMED IN LEEDS IN 1930-49 AND IN ENGLAND AND SCOTLAND IN 1956

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In this study the frequency of gastric, duodenal, and stomal ulcer has been determined in a survey at necropsy. This survey is likely to be much more accurate than those previously reported, as it has been a "forward planned" one and conducted by a group of men interested in this subject. In retrospective studies it is always impossible to know how carefully a particular point has been checked. It has been concluded from this study that the best estimate of the incidence of ulcer in the population as a whole can be made from the frequency of ulcers found in patients dying from causes other than peptic ulcer. The incidence of such active ulcers accords closely with clinical experience in life.

### THE LEEDS SURVEY 1930-49

Estimates of the incidence at necropsy of peptic ulcer are open to criticism on many grounds: pathologically, because the standard of examination must vary from hospital to hospital and from pathologist to pathologist as the pathological types and sites of ulcer have not been clearly distinguished, and duodenal scars are either missed or not thought worthy of record. Frequently, statistical principles are ignored in that all lesions from varying age groups are expressed as a single percentage with no regard for the age distribution of the ulcers found or the necropsy population at risk. The necropsy population may not give a true impression of hospital deaths because a varying fraction of the hospital deaths in different surveys is pathologically examined. The hospital population itself must be highly selected, reflecting the population served by the hospital, and the specialized interests and skill of the hospital staff. The reader is referred to the excellent critical appraisals of necropsy statistics published in 1950 by Ivy, Grossman, and Bachrach and by Levij (1959).

The many fallacies inherent in this type of analysis have discouraged pathologists from investigating further the incidence of ulcer; indeed a leading article published in the *Lancet* suggested that "the time and money spent on this type of examination could well be utilized in more profitable pastimes". However, there exists in many quarters a demand for estimates of ulcer frequency, and with notable exceptions incidence rates based on mortality statistics, clinical studies, food rationing figures, and social and industrial surveys limited by inadequate diagnostic methods are subject to as many limitations as are necropsy data. Necropsy statistics can be likened to corsets as undesirable, uncomfortable, frequently giving a fallacious impression of truth yet in special selected circumstances forming a basis for deduction, and at all times much sought after.

The data, presented in this paper with full awareness of their inadequacies, are produced because information has been collected from two sources, both unique, which to some extent reduce the defects in this type of investigation. They comprise first, the findings of one internationally acknowledged expert on ulcer incidence in one town, and, secondly, the findings of many pathologists in nine towns in England and Scotland in a forward-planned, concurrent investigation where particular care was taken to describe all ulcer lesions at hospital necropsies performed in 1956.

Over a 20-year period, between 1930 and 1949, necropsies performed in the Pathology Department of the University of Leeds have been analysed retrospectively by one observer. They were all performed under the close personal supervision of

the late Professor Matthew Stewart, whose contributions to the pathological study of peptic ulcer are well known. Stewart personally examined a large proportion of stomachs removed at necropsy, meticulously describing the ulcer lesions found, and inspiring in his staff a vigorous interest in the ulcer. The high standard of correlated clinical and pathological reports maintained in the department, the minute descriptions of the ulcers, particularly of ulcer scars, make this material almost unique for this type of survey. In Leeds a large proportion of the bodies of patients dying in hospital are examined at necropsy, 88% being examined in the 20-year period surveyed. The records will therefore indicate the pattern of hospital deaths during that time.

Secondly, a forward-planned, concurrent investigation of the incidence of ulcers at 11 teaching and seven non-teaching hospitals in London, Oxford, Bristol, Birmingham, Manchester, Leeds, York, Newcastle, and Glasgow was undertaken in 1956, so that it has been possible to estimate the national and regional frequency of ulcer. The data collected in both surveys formed the basis of a report to the conference on the geographical pathology of peptic ulcer held in Paris in 1957.

## Method of Recording and Analysis

The data were recorded on a proforma, listing age, sex, positive pathological findings, and the presence or absence of peptic ulcer. Deaths caused by ulcers and ulcers found incidentally were first distinguished, and the pathological type of ulcer specified as a chronic active ulcer, a chronic inactive ulcer or scar, an acute, or a subacute ulcer; acute erosions were excluded and chronic ulcer lesions were preferentially recorded in viscera in which several lesions were present. The site was indicated as gastric, duodenal, combined gastric and duodenal, stomal and oesophageal, and, finally, complications associated with the ulcer such as haemorrhage, perforation, cicatricial deformity, malignant change, and deaths following gastric surgery were enumerated.

Where a previous gastrectomy was discovered to have been performed an attempt was made to trace from the clinical records the site and type of ulcer for which the operation had been undertaken, but was not always possible, in which case the examination was included as a chronic ulcer unrelated to death.

In both surveys examinations which were incomplete or inconclusive were excluded, and cases of gastric carcinoma were omitted as the lesion frequently prevented adequate examination of the stomach and duodenum. The information recorded on a proforma was then transferred to a Powers-Samas punch card, double checked by independent operators and machine sorted.

Ulcer incidence was calculated as chronic active, chronic inactive, and combined inactive and active lesions, unrelated to and related to death, as a percentage incidence of the total necropsy population at risk in each age group. Adding these two groups gives the total incidence of chronic ulcer lesions in the survey. Seven age groups are included as follows: 0-24 years, 25-34 years, 35-44 years, 45-54 years, 55-64 years, 65-74 years, and over 75 years. The overall incidence of ulcer is reluctantly given for comparison with other surveys. It should be stressed, however, that this figure is almost valueless, depending as it does on the age distribution of the necropsy population at risk.

Probably the best estimate of the prevalence of ulcer in the general population is obtained by completely excluding all the ulcer deaths due to acute, subacute, or chronic ulcer from the necropsy population under consideration, and recording the incidence of chronic ulcer lesions found by chance in people dying in hospital for reasons other than ulcer. These are recorded as "incidental ulcer excluding ulcer deaths".

## Necropsy Population at Risk

Between 1930 and 1949, 15,130 deaths occurred at the Leeds General Infirmary and 13,314 necropsies were performed in the Pathological Department of the University of Leeds representing 87·9% of the hospital deaths. After 206 records (1·5%) had been rejected as inadequate, incomplete, or inconclusive, and 468 deaths from gastric carcinoma had been excluded, 12,640 records remained for analysis, representing 83·5% of the hospital deaths in that period and 94·9% of the necropsies performed. Seven thousand, seven hundred and twenty-two males and 4,918 females are included.

In the 1956 national survey, 7,290 records were submitted for analysis in Leeds, 19 were rejected as incomplete, inconclusive, or inadequate (0·3%), and 184 patients with gastric carcinoma were excluded, leaving 7,087 records for analysis comprising 4,151 males and 2,936 females.

Wide variation in the age distribution in the population at risk was apparent between hospitals, between towns, and between the 1956 and Leeds survey (Table I). These differences reflected varying obstetric, casualty, and geriatric facilities in the hospitals concerned and improved methods of treatment of acute infections and accidents, together with a reduced operative mortality in the two decades

TABLE I

PERCENTAGE AGE DISTRIBUTION OF NECROPSY POPULATIONS STUDIED

| Sex | Survey | −25 years | 25-34 years | 35-44 years | 45-54 years | 55-64 years | 65-74 years | 75+ years | Total |
|---|---|---|---|---|---|---|---|---|---|
| Males | Leeds, 1930-49 | 25·4 | 7·3 | 9·5 | 15·4 | 21·3 | 16·3 | 5·8 | 7,722 |
| | National, 1956 | 14·3 | 3·3 | 6·2 | 14·0 | 24·1 | 24·8 | 13·3 | 4,151 |
| Females | Leeds, 1930-49 | 27·9 | 7·2 | 9·6 | 15·1 | 19·4 | 15·5 | 5·4 | 4,918 |
| | National, 1956 | 14·4 | 4·1 | 6·4 | 12·1 | 20·4 | 23·8 | 18·9 | 2,946 |

between the two surveys. Age distribution differences, neglected in so many of the published reports, must be allowed for if any single overall figure for ulcer in two populations is being compared. The percentage age distribution of the two populations studied is shown in Table I.

## COMPARISON OF OCCURRENCE OF ULCERS IN THE TWO SURVEYS

The relative overall frequency of the lesions is compared in Table II. In this and in all succeeding tables, the ulcer incidence in the national survey has been corrected for variation in age distribution in

TABLE II

COMPARISON OF OVERALL INCIDENCE OF ULCER IN TWO SURVEYS

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Leeds 1930-49 | National 1956 | | Leeds 1930-49 | National 1956 | |
| Necropsy population | 7,722 | 4,151 | | 4,918 | 2,936 | |
| | Observed | Observed | Corrected | Observed | Observed | Corrected |
| Total ulcer, all types | 1,628 (21·1%) | 630 (15·2%) | 531·9 (12·8%) | 541 (11%) | 283 (9·7%) | 233·5 (7·9%) |
| Total chronic ulcer | 1,415 (18·4%) | 518 (12·5%) | 433 (10·4%) | 433 (9·5%) | 184 (6·3%) | 144·8 (4·9%) |
| Chronic active ulcer | 761 (9·9%) | 302 (7·3%) | 251·7 (5·7%) | 166 (3·4%) | 108 (3·7%) | 80·5 (2·7%) |
| Chronic inactive ulcer | 654 (8·5%) | 180 (4·3%) | 148·1 (3·6%) | 267 (6·2%) | 63 (2·2%) | 45·0 (1·5%) |
| Acute and subacute ulcer | 213 (2·7%) | 112 (2·7%) | 98·9 (2·4%) | 108 (2·2%) | 99 (3·4%) | 88·7 (3·0%) |

TABLE III

STATISTICAL COMPARISON OF OVERALL ULCER INCIDENCE IN THE TWO SURVEYS

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Leeds 1930-49 | Corrected National 1956 | $\chi^2$ n = 1 | Leeds 1930-49 | Corrected National 1956 | $\chi^2$ n = 1 |
| Necropsy population | 7,722 | 4,151 | — | 4,918 | 2,936 | — |
| Total chronic ulcer | | | | | | |
| Active | 761 (9·9)† | 252 (6·1) | $\chi^2$ = 45·176* P < 0·001 | 166 (3·4) | 87 (2·9) | $\chi^2$ = 1·078 P = 0·3 |
| Inactive | 654 (8·5) | 148 (3·6) | $\chi^2$ = 96·902* P < 0·001 | 267 (6·2) | 48 (1·7) | $\chi^2$ = 66·390* P = < 0·001 |
| Chronic duodenal ulcer | | | | | | |
| Active | 425 (5·5) | 137 (3·3) | $\chi^2$ = 28·147* P < 0·001 | 72 (1·5) | 31 (1·1) | $\chi^2$ = 2·641 P < 0·2 |
| Inactive | 472 (6·1) | 83 (2·0) | $\chi^2$ = 99·640* P < 0·001 | 160 (3·3) | 29 (1·0) | $\chi^2$ = 16·425* P < 0·001 |
| Chronic gastric ulcer | | | | | | |
| Active | 186 (2·4) | 93 (2·2) | $\chi^2$ = 0·393 P < 0·7 | 65 (1·3) | 39 (1·3) | $\chi^2$ = 0·0001 P < 0·99 |
| Inactive | 119 (1·5) | 59 (1·2) | $\chi^2$ = 0·222 P < 0·7 | 80 (1·6) | 16 (0·5) | $\chi^2$ = 17·778* P < 0·001 |
| Combined ulcer | | | | | | |
| Active | 113 (1·5) | 10 (0·2) | $\chi^2$ = 39·937* P < 0·001 | 27 (0·6) | 4 (0·1) | $\chi^2$ = 8·698 P < 0·01 |
| Inactive | 61 (0·8) | 4 (0·1) | $\chi^2$ = 24·291* P < 0·001 | 26 (0·5) | 0·4 (0·01) | $\chi^2$ = 16·103* P < 0·001 |

* Results showing a significantly increased incidence. † Percentages increase in brackets.

the necropsy population examined to be directly comparable with the Leeds study. A similar overall incidence of acute and subacute ulcers was demonstrated in the 321 ulcers found in the Leeds survey and the 211 ulcers found in the national survey (Leeds, males 2·7%, females 2·2%; national, males 2·4%, females 3·0%). Chronic ulcer lesions, in contrast, are approximately twice as common in the Leeds figures compared with the national figures, in males 18·4% to 10·4% and in females 9·5% to 4·9%. The differences are most apparent in the incidence of inactive lesions, males 8·5% to 3·6% and females 6·2% to 1·5%, the gap in incidence narrowing when active lesions are considered, males 9·9% to 5·7% and females 3·4% to 2·7%. This difference will be studied in more detail later.

Fallacies in the comparison of necropsy statistics done at different times by different pathologists is

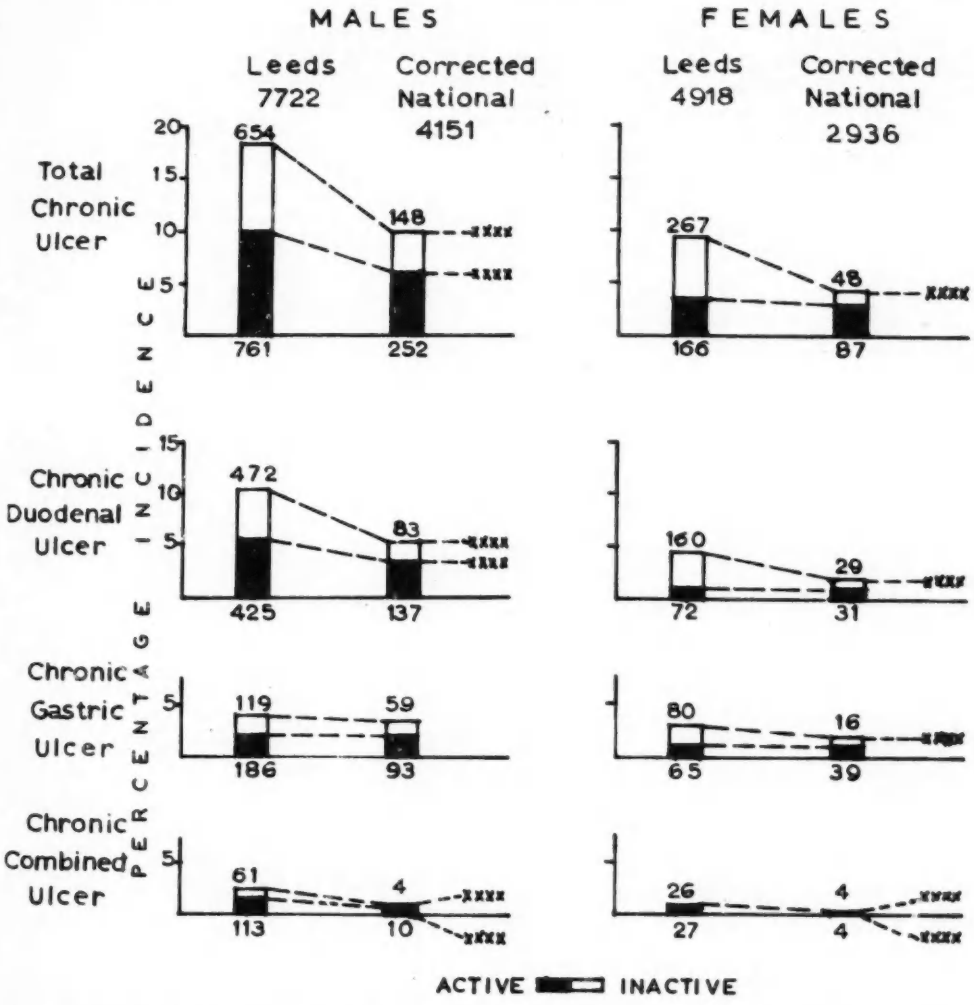


FIG. 1.—*The overall incidence of ulcer in the Leeds and national surveys.* P = < 0.05* < 0.02** < 0.01*** < 0.001****

well illustrated when the overall ulcer incidence in the Leeds figures is compared with the overall national figures in Table III, which shows that a highly significant increased incidence of chronic peptic ulcer is present in many of the Leeds figures compared with the corrected national figures (Fig. 1). In men, total, duodenal, combined, active and inactive lesions show highly significant differences in the two series, which are grossest for inactive duodenal lesions (6·1% to 2·0%) and mainly contribute to the significantly increased incidence of inactive lesions when all sites are considered together (8·5% to 3·6%). The occurrence of active gastric ulcer (2·4% and 2·2%) and gastric ulcer scars (1·5% and 1·2%) does not differ in the two series. In the combined ulcer lesions, where the recognition of minimal inactive duodenal lesions becomes important, significant differences are again observed, both ulcers and scars being approximately eight times more common in the Leeds series. In women again a highly significant increased incidence of ulcer scars is present for all types of ulcer which contribute to the total difference (6·2% as compared with 1·7%). The incidence of all types of active ulcer does not differ in the two series save for combined lesions, where active lesions show a sixfold and inactive lesions a 50-fold increase.

It at once emerges that inactive lesions have been found significantly more commonly in the Leeds survey, particularly duodenal scars and the combined gastric and duodenal lesions, gastric scars, for some reason, showing only an increased incidence in women. The possibility that the incidence of ulcer has declined in the eight years between the two surveys receives little clinical support. Evidence has been produced (Watkinson, 1958) suggesting an increased regional incidence in northern as compared with southern cities but this cannot wholly explain the differences. The difference must rest in the high standard of examination and the almost fanatical care with which duodenal scars were sought out and reported under Professor Stewart's direction in the Pathology Department of the University of Leeds. Therefore this series should give the most accurate appraisal of incidence.

The differences observed in active ulcers are less easily explained. The total occurrence in men of active ulcers is increased to a highly significant degree (6·1% to 9·9%), mainly contributed to by increases in duodenal and combined lesions. In women, however, there is no significant change in total (2·9% to 3·4%) or in duodenal ulcers (1·1% to 1·5%), combined lesions, however, showing a sixfold increase. The prevalence of active gastric ulcer in both men (2·4% and 2·2%) and in women (1·3% and 1·5%) agrees closely in the two series. Had observer error been wholly to blame one would not have expected to have found a significantly increased incidence of active duodenal ulcers in men and not in women, nor a significant increase in gastric scars in women and not in men, and these may well represent true regional variations.

The wide discrepancies in the occurrence of ulcers in two surveys done under optimal conditions emphasize that comparison with other necropsy studies would be valueless, and for this reason a factual statement on ulcer incidence in the circumstances in which each survey was done will be made and only passing reference to its incidence in other surveys will be attempted. The differences which have emerged show that even though special care is taken to identify and report ulcer lesions, the standard of examination cannot match up to that of an enthusiast in his field. It may be that the incidence in Stewart's hands was too high and that the true frequency lies somewhere between the two groups of data presented.

## Incidence of Chronic Peptic Ulcer in the Leeds Survey 1930-49*

The incidence of the various types of peptic ulcer causing and unrelated to death in the Leeds survey is shown in Figs. 2-6.

All Peptic Ulcers.—The occurrence of all peptic ulcer lesions found incidentally and causing death in men and in women is illustrated in Fig. 2.

The 1,415 ulcer lesions described in men were demonstrated in 18·4% of necropsy examinations, being active ulcers and scars in almost similar proportions, 9·9% and 8·5% respectively. These ulcers had caused 6·8% of the necropsy deaths and were found by chance in 11·5% of the examinations performed, scars being found incidentally twice as commonly as were active ulcers, 8·0% to 3·5%.

Ulcers caused most deaths in men between the ages of 45 and 54 years, and accounted for 13% of the necropsy deaths in that age group. The frequency declined in preceding and succeeding decades to 0·6% below 25 years and 2·7% above 75 years, and remained between 6·3% and 10·9% in the remaining age groups.

Ulcers were found by chance most commonly between the ages of 45 and 54 years, where approximately one in six men showed ulcer lesions. Ulcers occurred with almost uniform frequency in all age groups after 35 years, the incidence varying between

* Copies of tables enumerating precise percentages of ulcer frequency have been deposited at the libraries of the Royal Society of Medicine and the British Medical Association in London from which this information can be obtained. Alternatively the author may be approached directly.

13·0% and 16·6%. Active and inactive lesions followed similar distributions, active ulcers being demonstrated fortuitously in approximately one in 20 men above the age of 45 years. The varying age distribution of the ulcer deaths and ulcers found incidentally must represent selection in the type of case admitted to hospital rather than any lessening of ulcer mortality with age.

The perhaps unwise combination of ulcers causing and unrelated to deaths serves only to emphasize the frequency of peptic ulcer in middle-aged men where between one in three (29·2%) and one in four (24·1%) showed ulcer lesions.

When ulcer deaths are excluded from consideration ulcers were found incidentally in approximately one in seven men (14·2%) dying in hospital in Leeds from causes other than ulcer, one in 25 (4·3%) having an active ulcer at death. The age distribution of the ulcers found incidentally in men and women is shown in Fig. 3. Ulcers are found by chance in one in every five or six middle-aged or elderly men dying in hospital in Leeds exclusive of ulcer deaths (15·5% to 23·0%), approximately one in every 17 having active ulcers (4·1% to 7·1%).

The 433 ulcer lesions demonstrated in women (Fig. 2) occurred with only half the overall frequency of those in men, namely in 9·5% of post-mortem examinations, 91 accounted for 2·6% of the necropsy deaths, while 342 were found incidentally in 6·9% of the examinations. Ulcer scars were found twice as frequently as were active ulcers (6·2% to 3·4%). Fig. 2, which illustrates the age distribution of the ulcers in women, demonstrates the tendency, particularly for ulcer deaths and incidental active ulcers, to increase in frequency with advancing age. Ulcer scars found by chance doubled in frequency, from 3·3% to 7·4%, between the ages of 35 and 45 years. Ulcers caused most deaths (3·7%), and were found most commonly fortuitously between the ages of 65 and 74 years when approximately one in eight women were affected. The best estimate of ulcer frequency in the general population after ulcer deaths had been excluded would suggest that approximately one in 10 women between the ages of 35 and 44 years had suffered from peptic ulcer, one in 50 having active ulcers. This figure increased in elderly women to one in seven, of whom half had active lesions (Fig. 3).

When the relative sex incidence of peptic ulcers is studied ulcers caused roughly two and a half

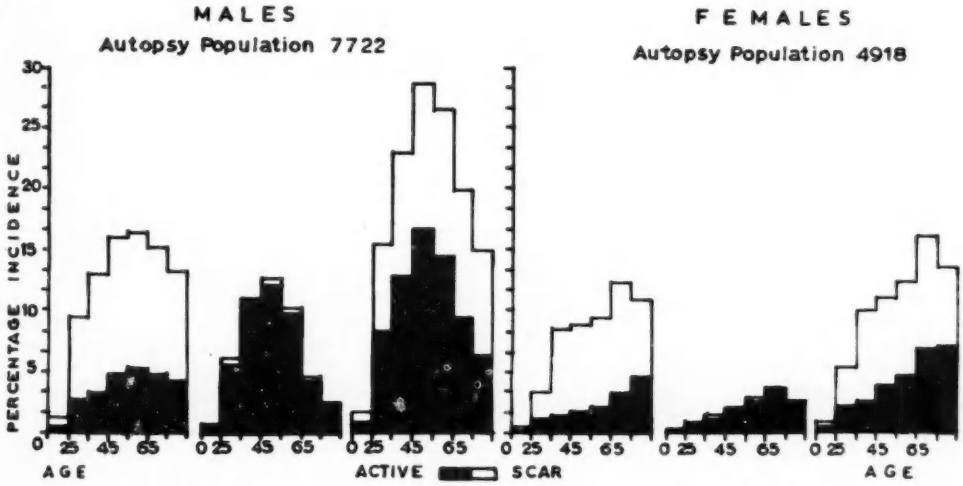


FIG. 2.—*The observed percentage frequency of all types of chronic ulcer at necropsy in Leeds between 1930 and 1949.*

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Ulcers Unrelated | Ulcer Deaths | Total Ulcers | Ulcers Unrelated | Ulcer Deaths | Total Ulcers |
| Active | 271 (3·5%) | 490 (6·3%) | 761 (9·9%) | 79 (1·6%) | 87 (1·8%) | 166 (3·4%) |
| Scars | 619 (8·0%) | 35 (0·4%) | 654 (8·5%) | 263 (5·4%) | 4 (0·1%) | 267 (6·2%) |
| Total | 890 (11·5%) | 525 (6·8%) | 1,415 (18·4%) | 342 (6·9%) | 91 (2·6%) | 433 (9·5%) |

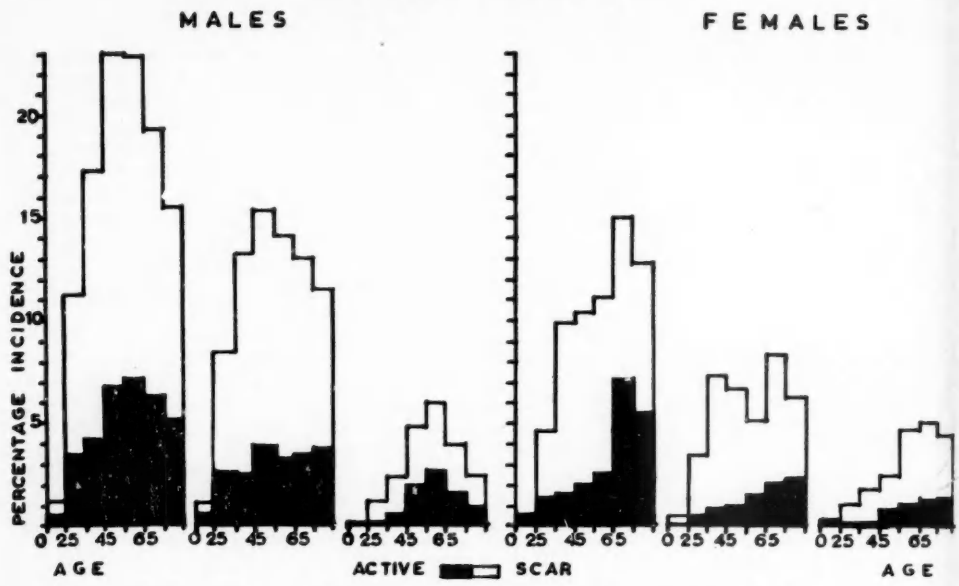


FIG. 3.—*The best estimate of ulcer frequency in the general population in Leeds, namely the incidence of ulcers after the highly selected group of ulcer deaths had been excluded from consideration.*

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Total | Duodenal Ulcer | Gastric Ulcer | Total | Duodenal Ulcer | Gastric Ulcer |
| Active | 271 (4·3%) | 153 (2·4%) | 72 (1·2%) | 79 (1·8%) | 37 (0·83%) | 26 (0·58%) |
| Scars | 619 (9·9%) | 451 (7·2%) | 107 (1·7%) | 263 (5·9%) | 158 (3·5%) | 79 (1·8%) |
| Total | 890 (14·2%) | 604 (9·6%) | 179 (2·9%) | 342 (7·7%) | 195 (4·4%) | 105 (2·3%) |

times more ulcer deaths in men than in women, a ratio of 2·63 to 1. Ulcer deaths occurred between six and eight times more commonly in young and middle-aged men than in women of the same age groups. Ulcer deaths increased sufficiently in frequency in elderly women so as to eliminate the sex difference by the age of 65 years.

Ulcer scars were found by chance one and a half times more often in men as compared with women, while incidental active ulcers were discovered twice as often. Again the male preponderance is most marked in the young and middle-aged, and lessened above the age of 65 where ulcer lesions were found with almost similar frequency.

CHRONIC DUODENAL ULCER.—The overall and age distribution of the 897 chronic duodenal ulcer lesions found in men and the 232 ulcers in women is shown in Fig. 4. In men chronic duodenal ulcer lesions were found in one in nine (11·6%) of the necropsies performed, caused one in 25 (3·8%) of the necropsy deaths, and were found incidentally in one in 12 necropsies (7·8%). Three times as many ulcer scars were found by chance as were active ulcers, relative frequencies being 5·8% to 2·0%, a similar ratio being maintained when ulcer deaths had been excluded, namely 7·2% to 2·4%. The 640 ulcer lesions, found incidentally after the exclusion of ulcer deaths, suggested that slightly more than one in 10 men (9·6%) in the hospital population studied had suffered from chronic duodenal ulcer.

Duodenal ulcers caused approximately one in 16 of the hospital deaths in men between the ages of 35 and 64 years with almost similar frequency in each of the decades included. Deaths due to this cause were less common in the young, 0·5% and 4·0%, and in the elderly, 2·4% and 1·1%.

Ulcers found by chance in men followed a distinctive age distribution, rapidly reaching a frequency of approximately one in 10 necropsies by the age of 35 years and showing a similar frequency with

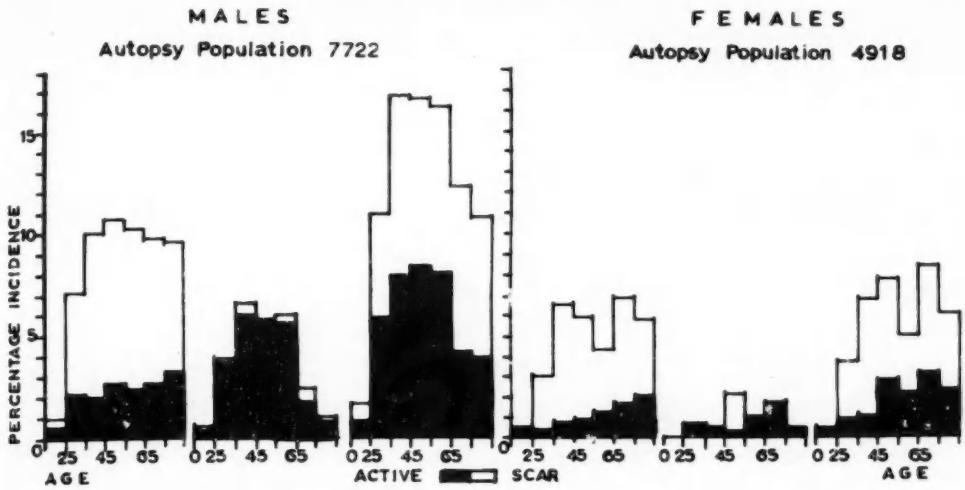


FIG. 4.—*The incidence of chronic duodenal ulcer lesions discovered at necropsy in Leeds between 1939 and 1949.*

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Ulcers Unrelated | Ulcer Deaths | Total Ulcers | Ulcers Unrelated | Ulcer Deaths | Total Ulcers |
| Active | 153 (1·9%) | 272 (3·5%) | 425 (5·5%) | 37 (0·7%) | 35 (0·7%) | 72 (1·5%) |
| Scars | 451 (5·8%) | 21 (0·3%) | 472 (6·1%) | 158 (3·2%) | 2 (0·4%) | 160 (3·3%) |
| Total | 604 (7·7%) | 293 (3·8%) | 897 (11·6%) | 195 (3·9%) | 37 (1·1%) | 232 (4·8%) |

advancing age in all subsequent decades, active ulcers being found in approximately 3% and ulcer scars in 8% of the necropsy population. Combination of the data revealed that approximately one in six men, in middle age, had suffered from or died from duodenal ulcers. When ulcer deaths had been excluded to give the best possible estimate of ulcer frequency (Fig. 3), this figure fell to one in seven (15·3%) in middle age, and to one in nine (11·5%) in the elderly.

Chronic duodenal ulcers were found less often in women (Fig. 4), being demonstrated incidentally in one in 25 examinations. They accounted for one in 75 of female hospital deaths occurring with a combined overall frequency of one in 20 necropsies. Again, approximately four times as many ulcer scars were demonstrated as were active ulcers at 3·2% to 0·8%. When ulcer deaths had been excluded, it was estimated that approximately one in 23 women had suffered in their lives from ulcer, rather less than one in 100 (0·8%), having active ulcers at death. When age incidence was considered (Fig. 4) little reliance can be placed on the small number of deaths due to ulcer in women save that they occurred more commonly after the menopause. Of the 195 ulcers found by chance, a tendency for active ulcers to become more common with advancing age was demonstrated, ulcer lesions increasing from 0·3% at 25 to 1·9% over the age of 75 years. Ulcer scars, as in men, reached a peak frequency at the age of 35 years where approximately one in 16 showed lesions, the incidence being of a similar order subsequently at 3·1% to 5·3%. When the few ulcer deaths had been excluded (Fig. 3), active duodenal ulcers again showed a progressively increasing frequency with advancing age, increasing from 0·3% in the second decade to 2·2% in the seventh. The figures suggest that between one in 20 (4·9%) and one in 12 (8·2%) of middle-aged and elderly women have suffered from duodenal ulcer.

Duodenal ulcers caused approximately five times more deaths in men than in women and were found incidentally twice as often. This male dominance was most marked below the age of 45 years where approximately 20 times more deaths from ulcer occurred in men, the gap narrowing with advancing age to one and a half to one above the age of 65 years. Incidental ulcers were demonstrated between two and three times as commonly in men as in women in most age groups, differences being

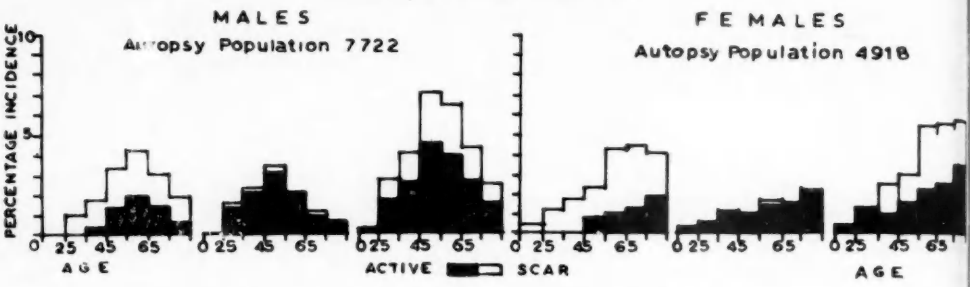


FIG. 5.—*Chronic gastric ulcer lesions demonstrated in the Leeds survey.*

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Ulcers Unrelated | Ulcer Deaths | Total Ulcers | Ulcers Unrelated | Ulcer Deaths | Total Ulcers |
| Active | 72 (0·9%) | 114 (1·5%) | 186 (2·4%) | 26 (0·5%) | 39 (0·79%) | 65 (1·3%) |
| Scars | 107 (1·4%) | 12 (0·2%) | 119 (1·5%) | 79 (1·6%) | 1 (0·2%) | 80 (1·6%) |
| Total | 179 (2·3%) | 126 (1·7%) | 305 (3·9%) | 105 (2·1%) | 40 (0·81%) | 145 (2·9%) |

most marked in the young, 2·9 : 1, and least marked in the elderly, 1·6 : 1.

CHRONIC GASTRIC ULCER.—The overall incidence and age distribution of the 305 gastric ulcer lesions demonstrated in men, together with the 145 lesions in women, is shown in Fig. 5.

Gastric ulcers or scars were demonstrated in approximately one in 25 of necropsies in males (3·9%) of which about one in 40 (2·4%) had active lesions. Gastric ulcers had caused 126 deaths (1·6%) and had been found incidentally in one in 40 necropsies, rather fewer than one in 100 having active ulcers. Excluding ulcer deaths, I would estimate that approximately one in 33 men (2·9%) in a hospital population have suffered from gastric ulcer, approximately one in 100 having active ulcers at death.

Gastric ulcers caused most deaths in men between the ages of 45 and 54 years (3·5%), the rate declining almost symmetrically in preceding and subsequent age groups. Gastric ulcers in women found incidentally and causing death were minimal in frequency with advancing age; particularly notable was the increase in incidental ulcer between the fourth and fifth decades, namely, 2·0% to 3·9%, remaining at this level in the elderly. This change is in keeping with the big rise of ulcer incidence, and complications frequently observed clinically in postmenopausal women. Estimates of the frequency of incidental gastric ulcer to the exclusion of ulcer deaths again confirmed that ulcer frequency doubled at this age. One in 45 women showed lesions in the fourth decade and one in 22 in the fifth decade, an increase of 2·3% to 4·6% (Fig. 3).

Comparison of ulcer recurrence in men and in women showed, for the first time, a less well-marked male predominance, the total lesions causing death and found incidentally being only slightly more common in men, in the ratio of 1·3 : 1. Ulcers still caused twice as many deaths in men as in women, 2·02 : 1, but were found incidentally with equal frequency, 1·1 : 1, active ulcers being found more often in men, 1·8 : 1, and scars in women, 0·9 : 1. Deaths due to gastric ulcer occurred three or four times more commonly in men than in women below the age of 55 years, but in the sixth and seventh decades occurred more commonly in women with frequencies of 0·96 and 0·3 to 1 respectively. A similar male predominance in ulcers found by chance occurred under 55 years, in the fourth decade ulcers being twice as common in men but gastric ulcers were found more frequently in elderly women, the ratio over 75 years being 0·5 : 1.

RELATIVE FREQUENCIES OF DUODENAL AND GASTRIC LESIONS.—When the frequency of duodenal to gastric lesions was investigated, in contradistinction to most necropsy series, a clear predominance of duodenal ulcer emerged most markedly in men and less so in women. Lethal and non-lethal duodenal ulcers were present approximately three times as commonly in men as were gastric ulcers and were almost one and a half times more common in women. Duodenal ulcers in men caused two to three times more deaths as did gastric ulcers. In women, however, deaths were more often due to gastric causes in the overall ratio of 0·9 : 1. When ulcer deaths were excluded, active duodenal ulcers were found twice as often in men

as were gastric, whereas four times as many duodenal scars were present, the relative frequencies being halved in women, the ratio active 1·1 : 1 and ulcer scars 2·0 : 1.

The greater proportion of deaths due to duodenal ulcer in men, though present in each age group, were most marked in the young and middle-aged where duodenal ulcers caused between three and four times more deaths than did gastric. In women the small numbers of deaths involved made differences between age groups unreliable, but again most premenopausal deaths in women were due to duodenal ulcers and most occurring after this time were due to gastric ulcer.

When ulcer deaths were excluded a clear-cut duodenal predominance was found in the incidental ulcers found in every age group in both men and in women. This was most marked in the young, relative frequencies in the first four age groups in men being approximately 21, 7, 6 and 3, to 1, and in women 7, 4, 4, 3 to 1 respectively. In middle-aged and elderly men duodenal lesions occurred three to five times as often but were only slightly more common in women of the same age group (1·1-1·7 : 1).

COMBINED GASTRIC AND DUODENAL ULCERS.—This not uncommon combination of ulcer lesions has caused much confusion in necropsy surveys; some pathologists have included the gastric and the duodenal lesions of the combined ulcers as additional single gastric or duodenal ulcers. This practice would artificially increase ulcer incidence in these sites, as more ulcers are reported than are necropsies performed, each lesion being counted twice. It was thought best to place combined lesions in a separate category, estimating their frequency independently.

One hundred and seventy-four combined gastric and duodenal ulcer lesions were found in men and 53 in women, relative overall frequencies being 2·3% and 1·1%; in men twice as many active as inactive lesions were found, namely, 1·5% to 0·8%. In women, however, they occurred with equal frequency, 0·55% and 0·53% respectively. These ulcers caused 73 deaths in men (0·9%) and 12 in women (0·2%). One hundred and one fortuitous lesions were found in men (1·3%) and 41 in women (0·8%). When ulcer deaths had been excluded, one in 50 males (1·6%) and one in 100 females (0·9%), dying in hospital from causes other than ulcer, showed combined gastric and duodenal lesions

TABLE IV

FREQUENCY OF ACTIVE ULCERS AND SCARS IN EACH SITE IN COMBINED GASTRIC AND DUODENAL ULCERS IN LEEDS SURVEY

| | Age Group Related | Both Active | | Active Gastric Ulcer and Duodenal Scar | | Active Duodenal Ulcer and Gastric Scar | | Gastric and Duodenal Scars | |
|---|---|---|---|---|---|---|---|---|---|
| | | Related | Unrelated | Related | Unrelated | Related | Unrelated | Related | Unrelated |
| MALES | −25 | — | — | — | — | — | — | — | 2 (0·11) |
| | 25− | 2 (0·36)* | 1 (0·18) | 2 (0·36) | 1 (0·18) | 1 (0·18) | 1 (0·18) | — | 4 (0·72) |
| | 35− | 2 (0·41) | 2 (0·27) | 5 (0·68) | 3 (0·41) | 1 (0·14) | — | 1 (0·14) | 4 (0·54) |
| | 45− | 10 (0·84) | 3 (0·25) | 6 (0·50) | 3 (0·25) | 3 (0·25) | 1 (0·08) | — | 15 (1·25) |
| | 55− | 7 (0·42) | 5 (0·30) | 15 (0·90) | 8 (0·49) | 3 (0·18) | 2 (0·12) | — | 18 (1·09) |
| | 65− | 4 (0·31) | 3 (0·23) | 4 (0·31) | 6 (0·45) | 2 (0·15) | — | — | 13 (1·02) |
| | 75 | 2 (0·43) | 1 (0·22) | 2 (0·43) | 1 (0·22) | — | — | — | 4 (0·86) |
| | | 28 0·36 | 15 (0·19) | 34 (0·44) | 22 (0·28) | 10 (0·13) | 4 (0·05) | 1 (0·01) | 60 (0·78) |
| FEMALES | −25 | 1 (0·07) | — | — | — | — | — | — | — |
| | 25− | — | — | — | — | — | — | — | — |
| | 35− | — | 1 (0·21) | — | 2 (0·42) | — | — | — | 1 (0·28) |
| | 45− | — | — | 3 (0·40) | 2 (0·27) | — | — | — | 1 (0·21) |
| | 55− | 1 (0·10) | — | 1 (0·10) | 2 (0·20) | — | — | — | 6 (0·67) |
| | 65− | 1 (0·13) | 2 (0·26) | 5 (0·75) | 3 (0·39) | — | — | — | 10 (1·05) |
| | 75 | — | — | — | 3 (1·13) | — | — | — | 6 (0·78) |
| | | — | — | — | | — | — | — | 2 (0·75) |
| | Total | 3 (0·06) | 3 (0·06) | 9 (0·18) | 12 (0·24) | — | — | — | 26 (0·53) |

* Percentage incidence in brackets.

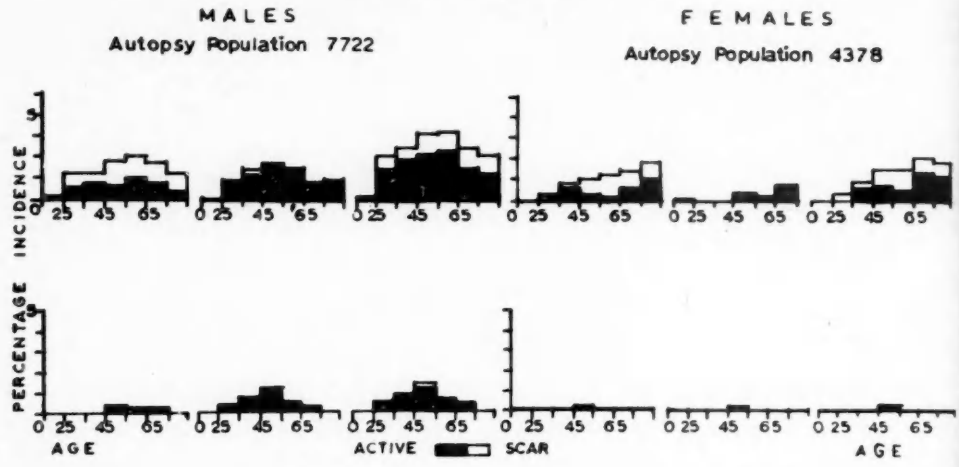


FIG. 6.—*The observed necropsy incidence of chronic combined gastric and duodenal ulcers (above) and of stomal ulcers (below) at necropsy in Leeds between 1930 and 1949.*

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Ulcers Unrelated | Ulcer Deaths | Total Ulcers | Ulcers Unrelated | Ulcer Deaths | Total Ulcers |
| Active | 41 (0·5%) | 72 (0·9%) | 113 (1·5%) | 15 (0·3%) | 12 (0·2%) | 27 (0·6%) |
| Scars | 60 (0·8%) | 1 (0·01%) | 61 (0·8%) | 26 (0·5%) | — | 26 (0·5%) |
| Total | 101 (1·3%) | 73 (0·9%) | 174 (2·3%) | 41 (0·8%) | 12 (0·2%) | 53 (1·1%) |
| *Chronic Stomal Ulcer* | | | | | | |
| Active | 3 (0·03%) | 30 (0·30%) | 33 (0·33%) | 1 (0·02%) | 1 0·02%) | 2 (0·04%) |
| Scars | 1 (0·01%) | 1 (0·01%) | 2 (0·02%) | — | — | — |
| Total | 4 (0·04%) | 31 (0·31%) | 35 (0·35)% | 1 (0·02%) | 1 (0·02%) | 2 (0·04%) |

(Fig. 6). The types of pathological lesion found in the two sites are summarized in Table IV.

Ulcer deaths due to combined ulcer were most common in men between the ages of 35 and 65 years and accounted for 1·5% of the necropsy deaths, while all 12 deaths occurred in postmenopausal women. Deaths in men were most often due to active lesions in both sites (0·4%) or to a chronic gastric ulcer with a duodenal scar (0·4%).

Ulcers found incidentally in men occurred most often between 45 and 74 years, when approximately one in 50 were affected and in the same age groups in women when the incidence had halved at 1·1% to 1·4%. Between 2·2% and 2·8% of middle-aged and elderly men dying in hospital, exclusive of ulcer, and between 1·2% and 1·7% of women in the same age group showed combined lesions. Scars in both sites were found incidentally as the most common pathological lesion in men and in women, the rate being 0·8% and 0·5% respectively. An active gastric ulcer with a duodenal scar occurred next most commonly (0·3% in men and 0·2% in women). Active ulcers in both sites were incidentally found with similar frequency in men (0·2%) but more rarely in women (0·06%), while the last possible combination of an active duodenal ulcer with a gastric scar appeared unique to men, causing 0·1% of deaths and being found incidentally in 0·05%.

Four times as many ulcer deaths occurred in men as in women, while incidental active ulcers and ulcer scars occurred most commonly in men at ratios of 1·7 and 1·5 : 1, respectively. Male incidental ulcers occurred twice as commonly in the fourth and fifth decades and only in elderly women were combined lesions more common, the rates being 0·7 : 1.

CHRONIC STOMAL ULCER.—Thirty-five chronic stomal ulcers were found in men (0·35%) and had caused death in 31 (0·3%) and two were demonstrated in women (0·4%). The overall and age distribution of the ulcers found is shown in Fig. 6. The small numbers involved make definite conclusions unwise but a similar pattern to that of

duodenal ulcer was obtained with a maximal incidence in middle life between 45 and 54 years.

OTHER ULCERS.—Chronic oesophageal ulcers were found in five men in the Leeds survey (0·05%) and had caused three deaths (0·03%), all save one occurring over the age of 65 years. No oesophageal ulcers were reported in women. By carefully tracing the clinical notes it was possible to determine the site and type of case for which incidental gastrectomies had been performed, ulcers being included under the appropriate headings. The few cases where this could not be traced or the type of ulcer classified were excluded from the study.

### FREQUENCY OF CHRONIC ULCER IN THE NATIONAL SURVEY IN 1956

The frequency of chronic peptic ulcers demonstrated in the national survey conducted in 1956 is indicated in similar fashion in Figs. 7-9, the incidence of all the lesions in men and women considered together being indicated in Fig. 7.

ALL CHRONIC ULCERS.—Five hundred and eighteen ulcers were found in 12·5% of the 4,151 necropsies reported, and active lesions were demonstrated twice as commonly as were ulcer scars, 7·2% to 4·3%. Ulcers had caused 185 necropsy deaths (4·5%), and had been found by chance in 333 necropsies (8·0%). When ulcer deaths had been excluded (Fig. 8) this survey would estimate that one in 12 men (8·3%) had at some time in their lives had a peptic ulcer, slightly more than half having healed ulcers at death, in that ulcer scars were found in 4·6% and active ulcers in 3·7% respectively.

When the age distribution of the ulcer deaths is considered, a differing pattern to the Leeds series was obtained; ulcer deaths in men reached a frequency of 4·3% by the age of 35 years, becoming more common with advancing age to 5·7% between 55 and 75 and 6·4% over 75 years, a pattern of ulcer deaths which conformed more to clinical experience than did the Leeds series. Ulcers were found incidentally most commonly in middle age when one in nine men showed ulcer lesions, one in 16 having scars at death. The figure only increased slightly to 10·5% to 12·0% when ulcer deaths have been excluded, more scars, 5·9% to 7·3%, being found than active ulcers, 4·0% to 4·7% (Figs. 7 and 8).

One hundred and eighty-four ulcer lesions were found in 6·3% of the 2,936 necropsies performed in

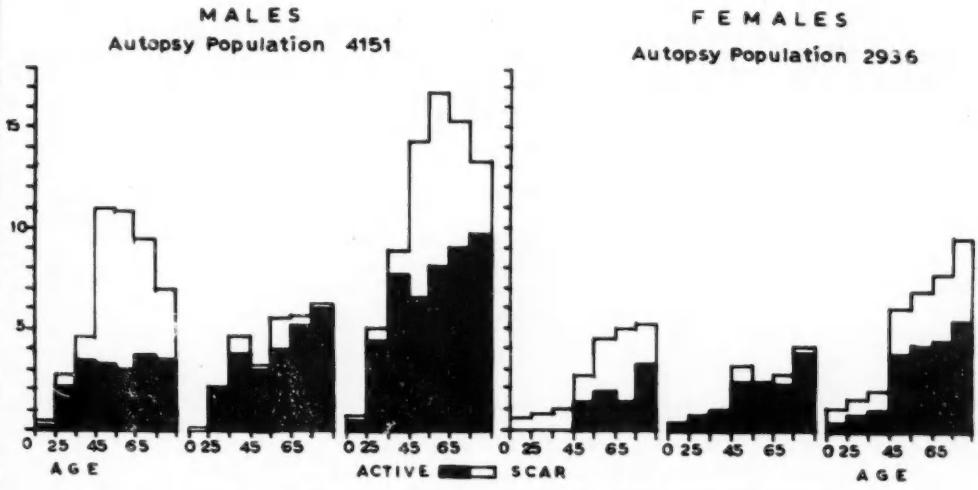


FIG. 7.—*The percentage frequency of all chronic ulcers demonstrated in the 1956 national survey.*

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Ulcers Unrelated | Ulcer Deaths | Total Ulcers | Ulcers Unrelated | Ulcer Deaths | Total Ulcers |
| Active | 133 (3·2%) | 169 (4·07%) | 302 (7·2%) | 41 (1·4%) | 67 (2·3%) | 108 (3·7%) |
| Scars | 166 (1·5%) | 14 (0·34%) | 180 (4·3%) | 56 (1·9%) | 7 (0·2%) | 63 (2·2%) |
| Total | 333 (8·02%) | 185 (4·46%) | 518 (12·5%) | 110 (3·7%) | 74 (2·5%) | 184 (6·3%) |

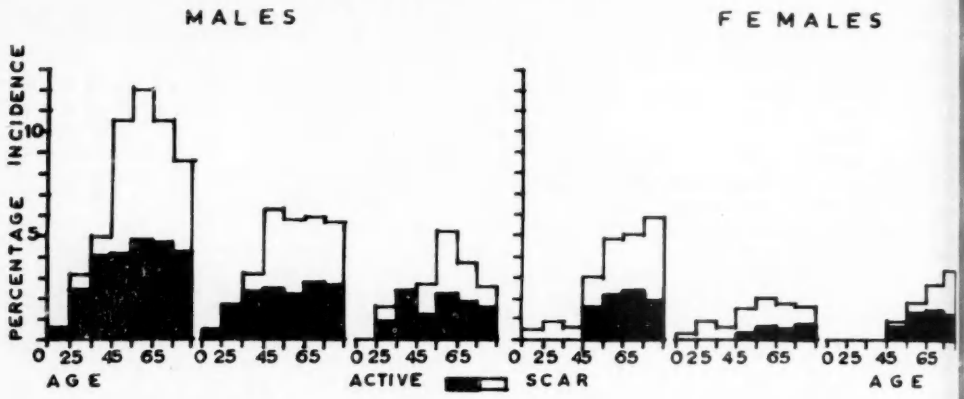


FIG. 8.—*The best estimate of ulcer frequency in 1956 in the general population as a whole, namely, the incidence of chronic peptic ulcer, excluding ulcer deaths.*

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Total | Duodenal Ulcer | Gastric Ulcer | Total | Duodenal Ulcer | Gastric Ulcer |
| Active | 133 (3·7%) | 72 (2·0%) | 49 (1·3%) | 41 (1·5%) | 9 (0·33%) | 24 (0·88%) |
| Scars | 166 (4·6%) | 93 (2·6%) | 56 (1·6%) | 56 (2·1%) | 28 (1·0%) | 23 (0·85%) |
| Total | 333 (8·3%) | 165 (4·6%) | 105 (2·9%) | 105 (3·9%) | 37 (1·4%) | 47 (1·7%) |

women, again more active lesions than ulcer scars being found, 3·7% to 2·2%. The 74 ulcer deaths in women accounted for 2·5% of necropsy deaths, an almost identical figure to that observed in Leeds. Of 342 ulcer lesions found incidentally in 3·7% of necropsies, similar proportions, 1·4% and 1·9%, were active and inactive lesions. When ulcer deaths had been excluded rather fewer than one in 25 women (3·9%) had at one time developed ulcers, while one in 66 (1·5%) had active lesions at death. When the age distribution of the lesions was considered (Figs. 7 and 8), although, as in the Leeds series, ulcers increased in frequency with age, the tendency for postmenopausal women to develop ulcers was more strikingly shown. In the third and fourth decades ulcer deaths in women trebled in frequency from 1·1% to 3·4%. Ulcers were found incidentally twice as commonly, 1·1% to 2·8%, and, if lethal and non-lethal ulcers are considered together, frequency is again trebled from 2·1% to 6·2%. Approximately one in 20 middle-aged or elderly women had at some time suffered from peptic ulcer (3·0% to 6·9%) while approximately one in 33 middle-aged and one in 23 elderly women had died from ulcers in the necropsy population studied.

Ulcers caused nearly twice as many deaths and were found by chance twice as often in men as in women. The small number of ulcers observed in women before the menopause make sex comparisons before this age unwise, but sex difference over 45 years become less apparent with advancing age, the male predominance reducing in successive decades to 3·9, 2·4, 1·9, and 1·3 : 1, respectively.

CHRONIC DUODENAL ULCER.—The frequency and age distribution of the chronic duodenal ulcer lesions found is illustrated in Fig. 9. In men, 263 ulcer lesions were found in 6·3% of the necropsy examinations conducted, of which 3·9% were active and 2·4% were ulcer scars. Ninety-eight duodenal ulcers had caused 2·4% of the necropsy deaths, while 165 were found incidentally in 4% of the examinations, being active ulcers or ulcer scars in almost similar proportions, 1·7% and 2·2%. The incidental finding of ulcer after ulcer deaths had been excluded would estimate duodenal ulcer frequency as one in 22 (4·5%) men, of whom one in 50 had active ulcers at death. The discrepancy of duodenal scars between the two surveys has already been commented on and can clearly be seen if Figs. 4 and 9 are compared, though the overall age distribution is similar.

As only eight deaths occurred in young men definite conclusions would be unwise, but it is of interest to note that the percentage of young men dying from this cause is only slightly less than in the

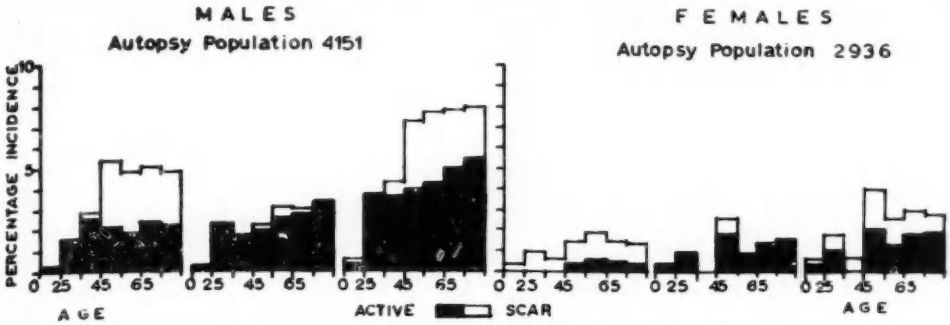


FIG. 9.—*Chronic duodenal ulcer lesions demonstrated in the national 1956 survey.*

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Ulcers Unrelated | Ulcer Deaths | Total Ulcers | Ulcers Unrelated | Ulcer Deaths | Total Ulcers |
| Active | 72 (1·7%) | 90 (2·2%) | 162 (3·9%) | 9 (0·3%) | 29 (0·9%) | 38 (1·3%) |
| Scars | 93 (2·2%) | 8 (0·1%) | 101 (2·4%) | 28 (0·9%) | 3 (1·0%) | 31 (1·0%) |
| Total | 165 (3·9%) | 98 (2·3%) | 263 (6·3%) | 37 (1·2%) | 32 (1·9%) | 69 (2·3%) |

middle-aged and elderly where ulcers caused 3·1% of all deaths. Ulcers, found by chance, occurred most commonly in middle-aged men of whom one in 19 had ulcers, the rate remaining at rather less than this frequency with advancing age. Active duodenal ulcers reached a frequency of one in 50 necropsies by 35 years and remained around this level in all succeeding decades. When ulcer deaths had been excluded, ulcer frequency in the fourth and subsequent decades approximated to one in 16 necropsies (5·6% and 6·2%) (Fig. 9).

The relatively small numbers of duodenal ulcers demonstrated in women will allow only limited conclusions. Sixty-nine ulcers were found in 2·3% of necropsies, active and inactive lesions being in similar proportions, 1·3% and 1·1%. Thirty-two duodenal ulcers had cause 1·1% of the necropsy deaths, while 37 (1·3%) had been found incidentally, the majority (0·9%) of which were healed. Again an increase in both fortuitous and lethal ulcers is demonstrated in postmenopausal women, when between one in 50 and one in 60 women show fortuitous lesions after ulcer deaths are excluded. An overall male predominance is again shown, both in ulcers causing death, 2·2 : 1, and ulcers found incidentally, 3·2 : 1, in the overall series, and in most age groups over 45 years.

CHRONIC GASTRIC ULCER.—The frequency and age distribution of the 175 gastric ulcer lesions found in men and the 79 demonstrated in women is shown in Fig. 10.

Gastric ulcers were the cause of death in 1·7% of male and 1·1% of female necropsies, being found incidentally in 2·5% and 1·6% of examinations respectively. As many ulcer scars as active ulcers were found in both sexes. Neglecting ulcer deaths, approximately one in 34 men (2·9%) and one in 59 women (1·7%) had developed gastric ulcers, half of which had healed before death in each instance.

Gastric ulcers became progressively more common with advancing age in women and were rarely observed in premenopausal women. Ulcer deaths doubled in frequency after the menopause, from 0·9% in the fifth decade to 2·2% in elderly women. Incidental ulcers more than trebled in frequency between the same two age groups, from 0·8% to 3·1%. Between one in 30 and one in 50 (1·8%-3·4%) of middle-aged and elderly women seemed to have had gastric ulcers in their life time when ulcer deaths had been excluded. In men, for some reason, gastric ulcers accounted for a disproportionately high fraction of 2·7% of deaths between 35 and 44 years, approximating to the number of deaths in men over 55 years, when one in 50 were affected (2·0%-2·7%). Ulcers were found fortuitously most commonly in the fifth decade when roughly one in 25 men showed gastric ulcer lesions (4.3%), rather less than half (1·8%) of which were active. When ulcer deaths were excluded, incidental ulcer lesions demonstrated in the hospital necropsy population would suggest that between one in 40 (2·6%) and one in 50 (5·2%) middle-aged and elderly men have at some time had gastric ulcers, of which

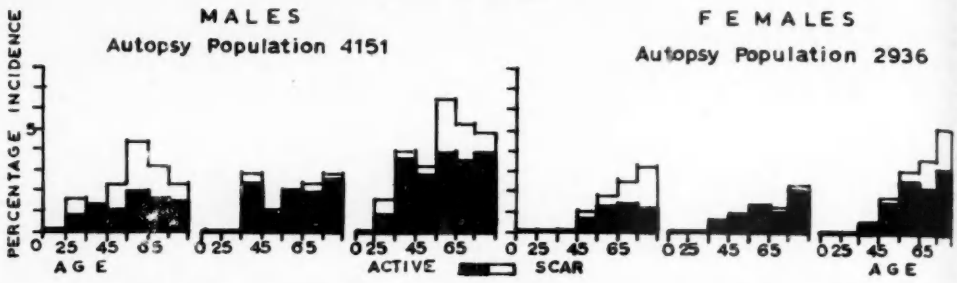


FIG. 10.—*The frequency of 175 chronic gastric ulcers found in men and 79 found in women in the 1956 survey.*

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Ulcers Unrelated | Ulcer Deaths | Total Ulcers | Ulcers Unrelated | Ulcer Deaths | Total Ulcers |
| Active | 49 (1·0%) | 65 (1·4%) | 114 (2·3%) | 24 (0·8%) | 29 (1·0%) | 53 (1·8%) |
| Scars | 56 (1·1%) | 5 (0·1%) | 61 (1·2%) | 23 (0·8%) | 3 (0·1%) | 26 (0·9%) |
| Total | 105 (2·1%) | 70 (1·5%) | 175 (3·5%) | 47 (1·6%) | 32 (1·1%) | 79 (2·7%) |

rather more than half had healed at death (Figs. 8 and 10).

The male predominance, common to most other types of ulcer, was less clearly shown for gastric ulcer and tended to disappear with advancing age. While two and a half times more gastric ulcers were demonstrated by chance in men than in women of 45 years old, this ratio dropped to 1·3 : 1 at 65, and in women over 75 years gastric ulcer was found more often in women giving a ratio of 0·71 : 1. More ulcer deaths occurred in men than in women in all age groups.

RELATIVE FREQUENCIES OF DUODENAL AND GASTRIC ULCERS.—As in the Leeds series, in men duodenal ulcers were found incidentally approximately twice as commonly as gastric ulcers, 1·9 : 1, and caused one and a half times more deaths, 1·6 : 1, this ratio holding good for most age groups over middle age. In women, although duodenal lesions were more common in middle age, causing three times more deaths and being found incidentally 1·7 times as frequently, the ratio fell in the elderly when more deaths are due to gastric ulcer, 0·7 : 1, and more were found incidentally, 0·4 : 1. When all ulcers were considered together regardless of age distribution, as many ulcer deaths resulted from gastric as from duodenal ulcer, while more gastric than duodenal lesions were found incidentally, 0·8 : 1.

COMBINED GASTRIC AND DUODENAL ULCER.—Seventeen combined gastric and duodenal ulcers were found in men in 0·3% of necropsies performed and six were found in women in 0·2%. These ulcers had caused five deaths in men (0·1%) and three in women (0·1%), and were found incidentally in 0.2% of male and in 0·1% of female necropsies. In both sexes no lesions were observed incidentally before 45 years or caused death before 55 years. The significant reduction from the Leeds series has already been commented upon, resulting from a paucity of duodenal ulcer scars (Table IV).

OTHER ULCERS.—Seven chronic stomal ulcers were reported in the national series (0·1%) and had caused five ulcer deaths (0·1%), all in subjects over 45 years. Three oesophageal ulcers were reported in men and had caused two deaths (0·04%) and five were reported in women causing four deaths (0·1%). The 21 men and six women who had undergone gastrectomy for peptic ulcer, and 15 men and seven women in whom the ulcer site was not stated, are included in the appropriate age group as chronic ulcers unrelated to death.

## DISCUSSION

The information obtained in the two surveys illustrates that even though particular care was taken to report peptic ulcer lesions, significant differences in estimating ulcer incidence emerged when ulcer frequencies were compared. Some were explicable by observer error, others by possible geographical differences in ulcer incidence, and others by varying policies relating to admission and medical practice in different hospitals. While the incidence of the grosser pathological lesions agreed closely in the two studies, it was in the reporting of ulcer scars that striking differences emerged, showing that careful routine pathological examination of the stomach and duodenum seemed insufficient to

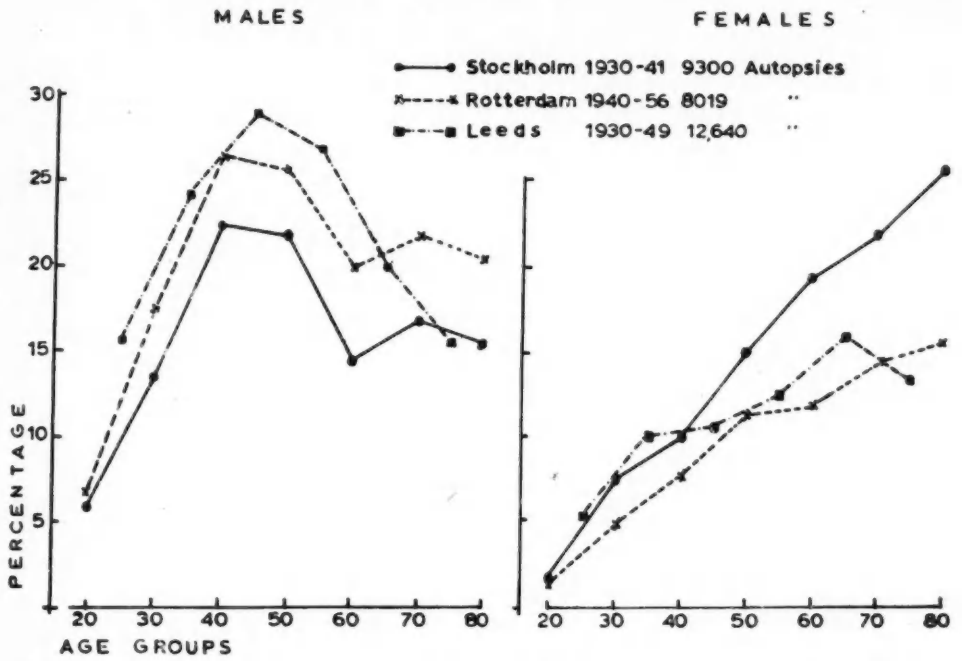


FIG. 11.—*The percentage frequency of chronic peptic ulcer causing death and found incidentally in 30,000 necropsy examinations performed in Stockholm, Rotterdam, and Leeds at varying periods between 1940 and 1956 (Falconer, 1943; Levij and Straub, 1957.)*

demonstrate all lesions, and that a particular specialized interest, such as was shown by Professor Stewart and his colleagues in Leeds, would demonstrate far more. For this reason, a factual statement of ulcer frequency has been presented in the circumstances in which each survey was performed and no attempt has been made to compare one with the other, nor with other surveys previously reported. The statistical fallacies of necropsy surveys have been described, particularly the limited value of overall estimates of ulcer frequency which take no account of the age distribution of the ulcer or necropsy population at risk.

It has been thought permissible to allow a limited comparison of the Leeds figures with two other necropsy studies performed over the same period, in which acute and chronic ulcer lesions were distinguished and ulcer deaths enumerated. Particular care was taken to find all ulcer lesions and careful statistical principles were observed throughout. A comparison with studies of 9,300 necropsies performed in Stockholm between 1930 and 1941 (Falconer, 1943) and 8,019 necropsies performed in Rotterdam between 1940 and 1956 (Levij and Straub) is made in Fig. 11, where both lethal and non-lethal chronic ulcers are included.

The strikingly similar age distribution of ulcer lesions in the three towns, showing a peak frequency in men between 40 and 50 and becoming more common with advancing age in women, suggests at least some uniformity in ulcer incidence in these European cities at this particular period.

Further discussion will be limited to reiterating what is thought to represent the best estimate of ulcer frequency in the population as a whole, namely ulcers found by chance in patients dying in hospital from causes other than ulcer and excluding ulcer deaths from consideration (see Figs. 3 and 8).

The Leeds survey (Fig. 3) would estimate that between one in four and one in six men (17·4% to 23·0%) over the age of 35 years suffered from peptic ulcer, approximately one in 20 having active ulcers at death (4·1% to 7·1%). In the same age groups, approximately one in seven (13·0% to

15·3%) had duodenal, approximately one in 20 (2·3% to 5·9%) gastric, and about one in 50 combined gastric and duodenal ulcer lesions. Ulcers were found in the national 1956 survey with approximately half this frequency, although the age distribution of the lesions was similar and the frequency of active lesions comparable (Fig. 8). Ulcers occurred most commonly in subjects over 45 years of age, when approximately one in 10 men (8·2% to 12·0%) had ulcer lesions, of which half were active at death (4·0% to 4·7%). Elderly and middle-aged men in this survey showed duodenal ulcers in approximately one in 18 necropsies (5·6% to 6·2%) and gastric ulcers in about one in 30 necropsies (2·6% to 5·2%), while combined gastric and duodenal ulcers were only rarely encountered (0·5% to 1·0%). An overall predominance of duodenal ulcers compared with gastric is most marked in the young and least marked in the elderly, a fact which could be demonstrated in both surveys, duodenal ulcers being found three to five times more often in men in the Leeds survey and one and a half to two times more often in the national figures. These figures come near to the clinically observed predominance of duodenal ulcer and contrast with many previous necropsy series, where the complications more frequently attendant on gastric ulcers make them more commonly observed in hospital populations.

In women in both surveys, sharp increases in ulcer frequency occurred in pre- and post-menopausal women, increasing in successive decades from 4·5% to 9·7% in Leeds and 0·6% to 3·0% in the national figures. The overall frequency in middle-aged and elderly women was estimated at approximately one in eight women (10·1% to 14·7%) in Leeds and at the much lower frequency of one in 25 women (3·0% to 5·9%) in the national figures. While in Leeds duodenal lesions predominated in every age group, ratios of between 1·1 : 1 and 2·8 : 1 being observed in the national figures, gastric ulcers were more often encountered in the elderly, ratios reducing from 1·7 : 1 to 0·5 : 1 when duodenal and gastric lesions were compared. Duodenal ulcer frequency was estimated in middle-aged and elderly women at about one in 13 (5·0% to 8·2%) in Leeds and one in 55 (1·5% to 2·0%) in the national figures. Gastric ulcer frequencies, too, show striking discrepancies at one in 21 (4·3% to 4·8%) in Leeds and approximately one in 60 (0·9% and 3·4%) for the national figures. Combined gastric and duodenal ulcer lesions were observed in between one in 50 and one in 80 necropsies (1·2% to 2·2%) in the Leeds necropsies in postmenopausal women but were hardly ever observed in the national series (0·2%). An overall male predominance of ulcer lesions emerged in both surveys, approximately 2 : 1 for total and duodenal ulcers and approximately 1·3 : 1 for gastric ulcers, differences again being most marked in the young and middle-aged and least apparent in the elderly in whom gastric ulcers were more commonly observed in women.

The vast amount of accumulated data has been presented as briefly as is possible. True ulcer frequencies may well lie at levels somewhere between the estimated frequency of the two surveys, but it is felt that the particular care taken by Professor Stewart and his staff in Leeds to describe and report ulcer lesions make it likely that these figures approximate more nearly to the true ulcer frequency in the population as a whole.

My thanks are due first to the late Professor Matthew Stewart for placing his departmental and personal records at my disposal and his encouragement to undertake the investigation; secondly, to the pathologists enumerated below for submitting their records for analysis in the 1956 survey; thirdly, to Mr. Jack Teale and members of the Records Department of the Leeds General Infirmary who undertook the mammoth task of punching and sorting the record cards in both surveys; fourthly, to Professor R. E. Tunbridge, who extended facilities of the Department of Medicine in Leeds for the study. Mr. Harry Revell gave invaluable help in the analysis and calculation of the data and preparation of the figures, and Miss A. Padgett undertook the exacting typing of this report.

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## APPENDIX

### Hospitals and Pathologists Participating in the National Survey in 1956

*London:* Central Middlesex Hospital, Dr. C. Treip; St. Thomas's Hospital, Prof. W. G. Barnard and Dr. K. J. Martin; University College Hospital, Dr. R. A. B. Drury; King's College Hospital, Prof. H. A. Magnus and Dr. B. S. Cardell; Postgraduate Medical School, Prof. C. V. Harrison.

*Birmingham:* Queen Elizabeth Hospital, Dr. B. T. Davis.

*Oxford:* The Radcliffe Infirmary, Dr. A. H. T. Robb-Smith.

*Bristol:* The Royal Infirmary, Prof. T. F. Hewer.

*Leeds:* The General Infirmary, Dr. R. Carmichael, Dr. T. W. Sutherland, Dr. C. Wright, Dr. H. Thompson, Dr. I. M. P. Dawson; St. James's Hospital, Dr. W. Goldie, Dr. G. M. Bonser, Dr. W. Mitchell, Dr. J. A. Dossett.

*York:* The County Hospital, Dr. D. A. Slade and Dr. G. A. C. Summers; The City Hospital, Dr. O. Cameron; (analysis by Dr. C. N. Pulvertaft); York County Coroner.

*Newcastle:* The General Hospital, Dr. B. E. Tomlinson.

*Manchester:* The Royal Infirmary, Prof. C. Campbell.

*Glasgow:* Stobhill Hospital, Dr. J. Dick; Western District Hospital, Dr. G. M. Ritchie; Western Infirmary, Prof. D. F. Cappell; Glasgow pneumoconiosis cases, Dr. B. Lennox and Dr. Ferguson Smith.

*Gut*, 1960, **1**, 31.

# OBSERVATIONS ON BLOOD GROUP DISTRIBUTION IN PEPTIC ULCER AND GASTRIC CANCER

BY

R. DOLL, B. F. SWYNNERTON, and A. C. NEWELL

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There is increasing evidence that blood group substances play a rôle in the causation of disease or in the protective mechanism against it. This paper records the special liability for patients of blood group O to develop stomal ulceration. Other data studied failed to confirm previous work suggesting that in gastric ulceration or neoplasm blood group A was a characteristic of an antral lesion.

Observations in many countries have established that there is an association between possession of the various ABO blood groups and susceptibility to certain gastrointestinal diseases (Aird, Bentall, and Roberts, 1953; Roberts, 1957). The associations are, however, not strong and the greatest variation from the normal distribution of blood groups, that is, among persons with a duodenal ulcer, implies a difference between the susceptibility of the various groups of only about 40%. The differences could be explained if the blood group substances played some direct part in producing or protecting against the diseases in question. Alternatively, the associations may be indirect and reflect the existence of a common factor which is both responsible for the promotion of the disease and is associated with an abnormal distribution of groups. The fact that the differences are so small weighs, perhaps, against the causal hypothesis, but it may be that the blood group substance is only one of several different causal factors and that clinical subgroups could be isolated in which the association with the specific substances was more marked. For example, Brown, Melrose, and Wallace (1956) noted that the association with blood group O was more marked for stomal ulcers than for duodenal ulcers, and Billington (1956b) noted that the association with blood group A was more marked when cancer arose in the antrum or in the cardiac region of the stomach than when it arose in the body of the stomach.

If these and other similar findings could be confirmed they would strengthen the evidence for the causal hypothesis and they would also indicate a more fruitful field for the study of intra-family comparisons. At present, such comparisons have failed to show any appreciable difference between the blood group distribution of affected and unaffected members; the expected differences are, however, so small that very large numbers of subjects are required and the absence of a significant difference in the published results may be due to chance (Clarke, Evans, McConnell, and Sheppard, 1959).

TABLE I

NUMBER OF PATIENTS STUDIED AND SOURCE OF DATA

| Condition | Hospital | No. of Patients | Description of Patients* | Period |
|---|---|---|---|---|
| Stomal ulcer | Central Middlesex | 123 | All patients | 1944-58 |
| | St. James's, Balham | 148 | All patients | 1942-57 |
| | St. Mary's, Paddington | 19 | Surgical unit | 1950-57 |
| | West London | 10 | Surgical in-patients | 1947-57 |
| Duodenal ulcer | Central Middlesex | 564 | Patients treated surgically 1954-57 plus a few new cases examined personally by A.N., 1958 | 1954-58 |
| Gastric ulcer | Central Middlesex | 605 | Patients treated surgically or for haemorrhage plus patients under medical care of R.D. | 1950-57 |
| Gastric cancer | Central Middlesex | 414 | All patients | 1950-58 |
| | St. James's, Balham | 443 | All patients | 1950-57 |

* Patients excluded those (i) for whom blood group data were not available in the hospital notes or in the records of the pathological departments, and (ii) for whom the diagnosis was not established by radiographs, gastroscopy, operation, or necropsy.

## MATERIAL

In the present study, data have been collected from the records of patients treated at the Central Middlesex Hospital, Acton, supplemented by data for cancer of the stomach from St. James's Hospital, Balham, and by data for stomal ulcer from St. James's Hospital and from St. Mary's Hospital, Paddington, and the West London Hospital, Hammersmith. The numbers of patients for whom data have been collected and the sources of the material are shown in Table I.

## RESULTS

STOMAL ULCER.—The distribution of the ABO blood group among patients treated for stomal ulcer is shown in Table II, in comparison with the distribution among a series of duodenal ulcer patients treated at the Central Middlesex Hospital and a control series of 10,000 women attending antenatal clinics in north-west London (Discombe and Meyer, 1952). The proportion of group O subjects is higher among the stomal ulcer patients (60·3%) than among the duodenal ulcer patients (52·8%) or among the control patients (45·8%). In each case the difference is statistically significant (stomal ulcer against duodenal ulcer patients, $\chi^2 = 4{\cdot}25$, n = 1, $P = 0{\cdot}04$; stomal ulcer against control patients, $\chi^2 = 24{\cdot}80$, n = 1, $P < 0{\cdot}001$). From these data it can be estimated that the risk of developing a stomal ulcer among persons of group O is 1·74 times the risk among persons of group A $\left(\frac{181}{96}\Big/\frac{4578}{4219}\right)$ and the relative risk is 1·35 times greater than the corresponding risk of developing a duodenal ulcer $\left(\frac{181}{96}\Big/\frac{298}{214}\right)$.

A comparison between these results and those recorded at other centres is shown in Table III. In Table III the relative risk is shown for group O in comparison with the combined data for groups A, B, and AB, because of the small numbers in some of the series. Mean relative risks, weighted

TABLE II

DISTRIBUTION OF ABO BLOOD GROUPS AMONG STOMAL ULCER AND DUODENAL ULCER PATIENTS AND CONTROL SUBJECTS

| Disease Category | No. of Subjects Belonging to Group | | | | All Subjects |
|---|---|---|---|---|---|
| | O | A | B | AB | |
| Stomal ulcer: | | | | | |
| Central Middlesex | 72 | 38 | 8 | 5 | 123 |
| St. James's | 91 | 49 | 8 | 0 | 148 |
| St. Mary's | 11 | 6 | 2 | 0 | 19 |
| West London | 7 | 3 | 0 | 0 | 10 |
| All hospitals | 181 (60·3%) | 96 (32·0%) | 18 (6·0%) | 5 (1·7%) | 300 (100·0%) |
| Duodenal ulcer | 298 (52·8%) | 214 (37·9%) | 39 (6·9%) | 13 (2·3%) | 564 (99·9%) |
| Control subjects without disease | 4,578 (45·8%) | 4,219 (42·2%) | 890 (8·9%) | 313 (3·1%) | 10,000 (100·0%) |

TABLE III

ABO BLOOD GROUPS AMONG STOMAL ULCER PATIENTS IN COLLECTED SERIES* COMPARED WITH THE DISTRIBUTION AMONG CORRESPONDING GROUPS OF DUODENAL ULCER AND CONTROL PATIENTS

| Centre | No. of Stomal Ulcer Patients | | No. of Duodenal Ulcer Patients | | No. of Control Patients | | Relative Risk O : (A+B+AB) | |
|---|---|---|---|---|---|---|---|---|
| | Group O | Groups A+B+AB | Group O | Groups A+B+AB | Group O | Groups A+B+AB | Stomal Ulcer : Duodenal Ulcer | Stomal Ulcer : Controls |
| London[1] | 181 | 119 | 298 | 266 | 4,578 | 5,422 | 1·36 : 1 | 1·86 : 1 |
| London[2] | 9 | 2 | 111 | 86 | | | 3·49 : 1 | |
| York[2] | 21 | 15 | — | — | 983 | 1,079 | — | 1·54 : 1 |
| Newcastle[2] | 16 | 11 | 281 | 186 | 6,598 | 6,974 | 0·96 : 1 | 1·54 : 1 |
| Glasgow[4] | 55 | 24 | 947 | 695 | 3,177 | 2,721 | 1·68 : 1 | 1·96 : 1 |
| Mean weighted relative incidence | | | | | | | 1·41 : 1 | 1·82 : 1 |
| $\chi^2$ for difference from unity | | | | | | | 8·518 | 37·397 |
| n = 1, P | | | | | | | < 0·01 | < 0·001 |
| $\chi^2$ for homogeneity | | | | | | | 2·918 | 0·559 |
| n = 3, P | | | | | | | 0·30 to 0·50 | 0·90 to 0·95 |

[1] Present series.
[2] Aird, Bentall, Mehigan, and Roberts (1954) and Roberts (1957 and personal communication). The data from the Central Middlesex Hospital and St. James's Hospital, Balham, are excluded as these are largely included in the present series.
[3] Data for stomal ulcer patients provided by Pulvertaft (personal communication); control data collected from Leeds (Aird *et al.*, 1954).
[4] Brown *et al.* (1956).

* Data reported by Balint, Cooper, Price, Pulvertaft, and Swynnerton (1957) are not shown separately as they are all included in the present series from London and York.

according to the numbers of observations in each series, have been calculated according to Woolf's method (Woolf, 1955; Roberts, 1957). The combined results for all the centres show that the risk of developing a stomal ulcer among group O subjects is approximately 1·82 times the risk among persons of groups A, B, or AB (95% limits of probability, 1·50 to 2·22) and that the relative risk is approximately 1·41 times greater than the corresponding risk of developing a duodenal ulcer (95% limits of probability, 1·12 to 1·79). With both comparisons the variation between the results in the different series can reasonably be regarded as due to random fluctuations.

DUODENAL ULCER.—In several investigations, the data for duodenal ulcer patients have been examined to see whether the extent of the association with group O varied with the severity of the disease. Clarke, Cowan, Edwards, Howel-Evans, McConnell, Woodrow, and Sheppard (1955) and Buckwalter, Wohlwend, Colter, Tidrick, and Knowler (1956) distinguished medically and surgically treated cases, and Brown *et al.* (1956) examined separately those patients whose ulcers had bled or perforated. No evidence was obtained to suggest that there was likely to be a substantial difference between the different groups. In the present series the patients have been divided according to (1) the age at onset of symptoms, and (2), for those who were treated surgically, the age at operation. The results are shown in Table IV. The greatest proportion of group O subjects (60·6%) is found among the patients who were operated on at ages 55 years or older. There is, however, no evident trend with age either at operation or at onset, and the differences in the proportions of group O subjects are not statistically significant. If the association varied with the severity of the disease it might be expected that the association would be strongest among patients in whom the disease appeared early or necessitated operation at an early age, and it seems, therefore, most likely that the present results are due to random fluctuation.

GASTRIC ULCER AND GASTRIC CANCER.—It has been demonstrated in many independent studies that the risk of developing a gastric ulcer is slightly greater for persons with blood group O than for persons with any of the other groups, while the risk of developing gastric cancer is slightly greater with blood group A. Data reported from 13 centres for nearly 4,000 gastric ulcer patients and over 6,500 gastric cancer patients have been reviewed by Roberts (1957), who estimated that the relative incidences of the two diseases among group O and group A subjects were 1·16 : 1 and 0·84 : 1 respectively. This interpretation of the data has, however, been contested by Billington (1956b) and by Balme and Jennings (1957). They suggest that the important association is between the *site* of the lesion and the blood group, and that the *nature* of the lesion, whether simple ulcer or carcinoma, is irrelevant. In their opinion, the overall association of carcinoma of the stomach with group A and of gastric ulcer with group O results from the fact that most carcinomas occur in the antrum where lesions are associated with group A, whereas most ulcers occur in the body of the stomach where lesions are associated with group O. In their experience, the relatively rare lesions of the cardia are associated with blood group A and are similar in this respect to lesions of the antrum. In the present series, gastric ulcers have been classified into three types according to whether the lesion occurred distal to the angulus or in the middle or upper third of the

TABLE IV

ABO BLOOD GROUPS AMONG DUODENAL PATIENTS DIVIDED ACCORDING TO AGE AT ONSET OF SYMPTOMS AND AGE AT OPERATION

| Characteristic | No. of Patients Belonging to Group | | | | All Patients | Relative Risk O : A |
|---|---|---|---|---|---|---|
| | O | A | B | AB | | |
| *Age at onset* | | | | | | |
| Under 25 years | 61 (53·0%) | 46 | 4 | 4 | 115 | 1·22 : 1 |
| 25-34 years | 85 (50·0%) | 65 | 15 | 5 | 170 | 1·21 : 1 |
| 35-44 years | 62 (49·2%) | 51 | 11 | 2 | 126 | 1·12 : 1 |
| 45 years and over | 84 (58·7%) | 48 | 9 | 2 | 143 | 1·61 : 1 |
| Age not known | 6 | 4 | 0 | 0 | 10 | — |
| *Age at operation* | | | | | | |
| Under 45 years | 102 (51·3%) | 76 | 14 | 7 | 199 | 1·24 : 1 |
| 45-54 years | 70 (47·9%) | 59 | 17 | 0 | 146 | 1·09 : 1 |
| 55 years and over | 97 (60·6%) | 54 | 5 | 4 | 160 | 1·66 : 1 |
| Not operated | 29 (49·2%) | 25 | 3 | 2 | 59 | 1·07 : 1 |
| All ages | 298 (52·8%) | 214 | 39 | 13 | 564 | 1·28 : 1 |

Age at onset:
Group O against groups A, B, and AB; $\chi^2 = 3{\cdot}21$, n = 3, $0{\cdot}3 < P < 0{\cdot}5$
Age at operation:
Group O against groups A, B, and AB; $\chi^2 = 5{\cdot}76$, n = 2, P = 0·07

stomach. Ulcers at the angulus of the stomach or at the junction of the middle and upper thirds have been classified as occurring in the middle zone. Cancers of the stomach were more difficult to locate, because by the time of diagnosis the disease had often spread beyond the zone in which it had arisen. In these circumstances, cancers were regarded as having arisen in the cardiac region only if the main bulk of the tumour was confined to the upper third of the stomach and in the antral region only if the main bulk was located distal to the angulus.

The distribution of blood groups associated with the two lesions in the different sites is shown in Table V. Despite the large number of cases the numbers in some of the subgroups are small and the differences between them may well be due to chance. The data for gastric ulcer would support the view that the association of this disease with blood group O is characteristic of ulcers of the body, but there is no evidence of a similar association for cancer of the stomach and there is very little evidence to suggest that lesions of the antrum are characteristically associated with group A. Other recent data have also failed to support the idea that the association is characteristic of the site of the lesion. In Johnson's (1957) series of gastric ulcers, the prepyloric ulcers showed the strongest association with group O and in Mosbech's (1958) large series of cases of gastric cancer, the ratios of groups O to A were practically the same irrespective of the site of origin of the disease. The published data for the two principal blood groups are summarized in Table VI. There are clearly wide differences between the results obtained in the different series and it is not possible to detect any consistent relationship between lesions in different parts of the stomach.

TABLE V

ABO BLOOD GROUPS IN GASTRIC ULCER AND GASTRIC CANCER PATIENTS DIVIDED ACCORDING TO SITE OF LESION

| Site | No. of Patients Belonging to Group | | | | All Subjects | Relative Risk O : A |
|---|---|---|---|---|---|---|
| | O | A | B | AB | | |
| *Gastric ulcer* | | | | | | |
| Upper third | 68 (54·0%) | 42 (33·3%) | 14 | 2 | 126 | 1·49 : 1 |
| Mid third | 180 (49·2%) | 150 (41·0%) | 25 | 11 | 366 | 1·11 : 1 |
| Antrum | 24 (45·3%) | 22 (41·5%) | 5 | 2 | 53 | 1·01 : 1 |
| Mixed sites or site uncertain | 31 | 26 | 3 | 0 | 60 | — |
| | 303 (50·1%) | 240 (39·7%) | 47 | 15 | 605 | 1·16 : 1 |
| *Gastric cancer* | | | | | | |
| Cardiac region | 49 (36·8%) | 65 (48·9%) | 15 | 4 | 133 | 0·69 : 1 |
| Upper half | 45 (42·9%) | 53 (50·5%) | 7 | 0 | 105 | 0·78 : 1 |
| Mid third | 50 (43·1%) | 53 (45·7%) | 9 | 4 | 116 | 0·87 : 1 |
| Lower half | 24 (40·7%) | 26 (44·1%) | 7 | 2 | 59 | 0·85 : 1 |
| Antrum | 132 (43·0%) | 125 (41·7%) | 30 | 13 | 300 | 0·97 : 1 |
| Whole body or site uncertain | 62 | 70 | 7 | 5 | 144 | — |
| All sites | 362 (42·2%) | 392 (45·7%) | 75 | 28 | 857 | 0·85 : 1 |
| Control subjects without disease | 4,578 (45·8%) | 4,219 (42·2%) | 890 | 313 | 10,000 | — |

Difference between O and A for gastric ulcers in the antrum compared with other parts of stomach $\chi^2 = 0{\cdot}297$, n = 1, $0{\cdot}5 < P < 0{\cdot}7$
Difference between O and A for gastric cancers in the cardiac region, mid-third of stomach and antrum $\chi^2 = 2{\cdot}141$, n = 2, $0{\cdot}3 < P < 0{\cdot}5$

TABLE VI

O AND A BLOOD GROUPS IN GASTRIC ULCER AND GASTRIC CANCER PATIENTS DIVIDED ACCORDING TO SITE OF LESION IN COLLECTED SERIES

| Authors | Site of Lesion | Gastric Ulcer | | | Gastric Cancer | | |
|---|---|---|---|---|---|---|---|
| | | No. in Group | | O/A | No. in Group | | O/A |
| | | O | A | | O | A | |
| Billington (1956a, 1956b) | Cardiac region | 94 | 47 | 2·00 | 24 | 50 | 0·48 |
| | Mid-body | | | | 154 | 47 | 3·28 |
| | Antrum | 22 | 52 | 0·42 | 53 | 96 | 0·55 |
| Balme and Jennings (1957) | Cardiac region | 76 | 67 | 1·13 | 15 | 22 | 0·68 |
| Jennings, Balme, and Richardson (1956) | Mid-body | | | | 41 | 42 | 0·98 |
| | Antrum | 20 | 29 | 0·69 | 33 | 64 | 0·52 |
| Johnson (1957) | Cardiac region | 127 | 111 | 1·14 | — | — | — |
| | Mid-body | | | | — | — | — |
| | Antrum | 59 | 32 | 1·84 | — | — | — |
| Mosbech (1958) | Cardiac region | — | — | — | 83 | 105 | 0·79 |
| | Mid-body | — | — | — | 203 | 271 | 0·75 |
| | Antrum | — | — | — | 311 | 387 | 0·80 |
| Doll, Newell, and Swynnerton (present data) | Cardiac region | 248 | 192 | 1·29 | 49 | 65 | 0·75 |
| | Mid-body | | | | 50 | 53 | 0·94 |
| | Antrum | 24 | 22 | 1·09 | 132 | 125 | 1·06 |

## Summary and Conclusions

Out of 300 patients with stomal ulcers, 181 (60·3%) belonged to blood group O; among 564 patients with duodenal ulcer, the proportion was 52·8%. From these and other published data, it can be estimated that the risk of developing a stomal ulcer is approximately 1·8 times greater among group O subjects than among subjects belonging to the other three groups (O : A + B + AB) and that the relative risk among group O subjects is approximately 1·4 times greater than the relative risk of developing a duodenal ulcer. The observation of a "biological gradient" between the frequency of blood group O and susceptibility to peptic ulceration may be regarded as support for the hypothesis that the blood group substances play a direct part in the causation of the disease, or in protecting against it.

Data for the duodenal ulcer patients failed to provide any evidence that the age of onset of symptoms or the age at operation was likely to be earlier among group O subjects; such differences as were observed were in the opposite direction and could be attributed to chance.

Data for 605 gastric ulcer patients and 857 gastric cancer patients were examined to see whether the frequency of blood groups O and A varied with the site of the lesion. The observed differences were not statistically significant and did not support the suggestion that the association with blood group A was characteristic of an antral lesion or that the association with blood group O was characteristic of a lesion of the body of the stomach.


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# THE EFFECTS OF CORTICOTROPHIN AND CORTICOIDS ON SECRETION FROM DENERVATED GASTRIC POUCHES IN DOGS*

BY

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The effects of corticotrophin and of cortisone, methyl prednisolone, and of aldosterone on the gastric secretion of dogs have been investigated. Juice was collected from dogs with denervated pouches under basal conditions and when stimulated with meat extract and with histamine. For each secretion the volume, viscosity, and *p*H were measured, and the concentrations of hydrochloric acid, pepsin, sodium, potassium, and chloride estimated.

In the pharmacological doses used all the substances produced similar effects. Volume and acidity of the secretion were increased and there was a decrease in the viscosity of the basal secretion. The concentration of pepsin and of sodium and potassium were decreased while the chloride concentration was unaffected. Cortisone (the only steroid tested in this respect) increased the maximal secretory response to histamine. Three to five days elapsed before any change took place in the secretion.

The effects observed were independent of the glucocorticoid or mineralocorticoid activity of the particular hormone used and were probably due in some measure to a 50% increase in parietal cell population, associated with a 36% decrease in peptic cell population, which was demonstrated histologically.

The relationship between the hormones of the adrenal cortex and the secretion of gastric juice is of interest for several reasons. It throws light on the pathogenesis of steroid-induced ulcers, it may be concerned in the development of simple peptic ulceration, and it is certainly of physiological importance. The nature of the relationship has been approached in various ways and those who have studied it have reported conflicting results.

Thus the effects of the administration of corticoids and of adrenalectomy, with and without replacement therapy, have been reported by several workers, while others have studied the structure and function of the adrenal cortices in patients with gastric disorders. We are mainly concerned here with the effects of the administration of corticoids, in pharmacological doses, on gastric secretion in all its aspects.

## Secretion of Acid

The effects of corticotrophin, cortisone, and other steroids on the stomach in man are uncertain. Some (Hirschowitz, Streeten, Pollard, and Boldt, 1955; Carbone and Liebowitz, 1958) have found that they stimulate acid secretion, while others (Winkelstein, 1957; Dreiling, Janowitz and Rolbin, 1958) have found that they do not. These discrepancies may be the result of differences in the doses which were used and in the length of time during which the substances were administered. The concentration of acid in gastric juice is increased in Cushing's syndrome and restored to normal by adrenalectomy (Kyle, Logan, Neill, and Welbourn, 1956). Corticotrophin and cortisone increase the secretion of acid in the monkey (French, Longmire, Porter, and Movius, 1953), but neither they nor deoxycortone have any stimulatory effect in the rat (Kyle and Welbourn, 1956).

The results of experiments carried out in the dog are no less conflicting. Some (Zubiran, Kark, and Dragstedt, 1952a; Zubiran, Kark, Montalbetti, Morel, and Dragstedt, 1952b) have found that a sustained increase in acid secretion from innervated and denervated pouches is produced by corticotrophin in a dose of 75 mg. per day for 10 days and by cortisone in a dose of 100 mg. per day for 30 days. Others (Wiederanders, Classen, and Gobbel, 1959) did not find any increase when they gave 300 mg. of cortisone daily for 10 days. Prednisolone is reported to stimulate acid production and to increase the

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volume of both basal and histamine-stimulated secretion from denervated pouches. The effects of corticotrophin and of corticoids given for short periods are also uncertain. Some (Ragins, Dragstedt, Landor, Lyon, and Dragstedt, 1956) did not observe any effects when massive doses of corticotrophin, cortisone, and hydrocortisone were given to dogs with denervated pouches. Others (Plainos and Phillippu, 1958; Villareal, Ganong, and Gray, 1955) found that corticotrophin increased the secretion by the intact stomach, and that the effect persisted after vagotomy. There is uncertainty also about the relationship of the gastric antrum to the hypersecretion produced by corticoids. Some (McGee, Blackburn, Lance, and Scott, 1959) have found that excision of the antrum abolishes the secretory response to cortisone. Others (Zubiran *et al.*, 1952a) report that antrectomy has no effect. Similarly antrectomy has no effect on the secretion induced by corticotrophin (Villareal *et al.*, 1955). Cortisone, instilled locally into denervated pouches, has no effect on secretion (McGee *et al.*, 1959).

### Secretion of Pepsin

There is no general agreement on the effects of adrenal steroids on the secretion of pepsin. Some workers have reported a rise in gastric pepsin and in uropepsin during the administration of corticotrophin (Gray, Benson, Reifenstein, and Spiro, 1951a; Gray, Benson, Spiro, and Reifenstein, 1951b; Hirschowitz *et al.*, 1955) and of prednisolone (Carbone and Liebowitz, 1958) in man and in the dog. Others have found no increase in gastric pepsin or in the pepsinogen of plasma or urine in human subjects when adrenal steroids are infused for short periods (Hirschowitz, London, and Pollard, 1957; Dreiling *et al.*, 1958). It may be, however, that the dosage and duration of administration determine the effect. Hydrocortisone, in doses of 40 mg. and 10 mg. per day respectively, have no effect, while the same steroids, given in doses twice this size, cause a definite increase in the excretion of uropepsin (Oka and Aho, 1957). It should be noted that the concentrations of pepsinogen in the plasma and in the urine may not reflect accurately the secretion of pepsin by the stomach. It has, for instance, been found that adrenal steroids increase the clearance of pepsinogen by the kidneys (Hirschowitz *et al.*, 1957).

### Secretion of Mucus

The effect of corticoids on the secretion of mucus does not appear to have been studied in detail. However, the visible mucus content and the viscosity of the gastric juice (which is related to the concentration of dissolved mucus) are reduced by corticotrophin and corticosterone but not by hydrocortisone (Hirschowitz *et al.*, 1955).

### Secretion of Electrolytes

Little work has been published on the effects of corticoids on the concentrations of sodium, potassium, and chloride ions in the gastric juice. In one study in the dog the chloride content was found to rise and the sodium and potassium concentrations to fall appreciably after a single injection of corticotrophin (Villareal *et al.*, 1955).

### Effects of Adrenal Insufficiency

Addison's disease in man is often associated with achlorhydria (Rowntree and Snell, 1931). In the rat (Welbourn and Code, 1953; Kyle and Welbourn, 1956) adrenalectomy reduces the volume and the acidity of gastric juice and cortisone subsequently not only restores the secretion but increases it to a supranormal level. Deoxycortone restores the volume, but not the acidity, of the juice after adrenalectomy.

In the dog adrenalectomy abolishes the gastric secretory response to corticotrophin.

The relationship between histamine-induced and corticoid-induced secretion has been studied after adrenalectomy. In a patient with Addison's disease (Stempien and Dagradi, 1954) very little gastric response to histamine was obtained. When cortisone, deoxycortone, and salt were given the response was greatly increased. In the rat (Kyle and Welbourn, 1956) histamine restores the volume and the acidity of gastric juice after adrenalectomy, but does not cause hypersecretion as it does in animals with intact adrenal glands. The restoration of secretion is brought about by a dose of histamine which is much smaller than that required to stimulate secretion in the normal animal. In the dog (Sigel, Bassett, and Cooper, 1957) the response of the stomach to histamine after adrenalectomy varies directly (within limits) with the dose of cortisone administered. A little secretion, however, is still obtained when cortisone is withdrawn. We may conclude that the gastric mucosa is capable of responding to histamine in the absence of endogenous or exogenous corticoids, but that corticoids are necessary for an optimal response.

Destruction of the pituitary in man (Escamilla and Lisser, 1942; Kyle, 1955) and in the rat (Kyle and Welbourn, 1956) reduces gastric secretion even more than does destruction of the adrenals.

### Possible Modes of Action

If, as seems probable from the weight of evidence, corticoids increase the secretion of acid by the stomach, we must ask how they do so. There are several possibilities:

(1) Corticoids sensitize the parietal cells to normal stimuli.

(2) They cause the liberation of histamine in the vicinity of the parietal cells. The level of histamine in the blood is reduced and the excretion of histamine in the urine is increased by the administration of cortisone (Code and Mitchell, 1953; Mitchell and Code, 1954; Kelemen and Bikich, 1956).

(3) They affect the exchange of electrolytes across the gastric mucosa in the same way as they do across the cells of the sweat glands and the renal tubules. If sodium ions were retained, there might be a compensatory increase in the excretion of hydrogen ions.

(4) They increase the number of parietal cells in the stomach.

## Present Investigation

This investigation, which was done in dogs with denervated gastric pouches, was undertaken with the following objects:

(1) To discover the effects of corticotrophin and of corticoids on the various components of gastric juice.

(2) To discover whether the maximal secretory response to histamine could be enhanced by cortisone.

(3) To elucidate the relationship between the secretion of hydrogen ions and that of other electrolyte ions. For this reason the effects of methyl prednisolone, a relatively pure glucocorticoid, and of aldosterone, a very strong mineralocorticoid, were compared with those of corticotrophin and cortisone. Cortisone itself has both glucorticoid and mineralocorticoid activity.

(4) To find the effect of corticoids on the cellular structure of the gastric mucosa.

## Materials and Methods

Eight smooth-haired mongrel bitches weighing 7-14 kg. were used in the "secretion" experiments (1-3 above). Denervated (Heidenhain) pouches were prepared and fitted with "duralumin" cannulae. The animals were not tested for at least five weeks after the operations. They were fasted for 18 hours before all tests. During the experiments control tests were made frequently.

Throughout the experiments (except when they were being fasted before a test) all the dogs were fed on a standard diet consisting of meal offal and pig starter meal in equal parts. Each dog was fed once daily with a measured quantity sufficient to provide approximately 70 Calories per kilogram per day.

Gastric juice was collected in graduated tubes, and the following estimations were made: (*a*) volume; (*b*) *p*H by a direct-reading *p*H meter; (*c*) free and total acid by titration against N/20 NaOH with Töpfer's reagent as indicator; (*d*) pepsin by the modified Mett method (Hawk, Oser and Summerson, 1952); (*e*) sodium and potassium by flame photometry; (*f*) chloride by the method of Schales and Schales (1941); (*g*) viscosity by measuring the time taken to fall a measured distance in capillary tubing of standard bore.

In some large specimens the protein content was estimated. The juice was dialysed and dried in a vacuum at −20°C. The solid residue was then weighed.

Collections of gastric juice were taken under three sets of conditions:

(1) Basal Secretion.—In these tests the gastric juice was collected for four hours from the unstimulated pouch.

(2) Antral Stimulation.—The gastric antrum was stimulated by the injection of meat extract (35 ml. of a 20% solution of "bovril" at *p*H 5·4) into the stomach through a polythene tube. A standard meat meal had been tried previously but was abandoned because many of the dogs refused to eat it when they were receiving corticoids. Collections were taken for half an hour after the injection.

(3) Histamine Stimulation.—Collections were made after (*a*) standard tests and (*b*) after injections to obtain the maximal secretory response.

(*a*) *Standard Tests.*—Histamine acid phosphate (B.P.) was injected subcutaneously in a dose of 1 mg. of histamine base per 10 kg. body weight. Half an hour before the administration of histamine 5 mg. of chlorpheniramine maleate (an antihistaminic drug) was given subcutaneously. Collections were taken for half an hour after the injection of histamine.

(*b*) *Maximal Secretory Response.*—The technique was similar to that described by Code (Code, Blackburn, Livermore, and Ratke, 1949). The antihistamine (5 mg.) was injected half an hour before the start of the test and again two and a half hours later. Gastric juice was collected for half an hour from the time of the first injection to ensure that the pouch was secreting at a basal rate. Histamine was then injected every 15 minutes through a polythene tube, which was left lying in the subcutaneous tissues. Each injection contained 0·17 mg. of histamine base initially and the dose was doubled every hour. The collecting tube was changed every 15 minutes and the test was stopped when an increase in the dose of histamine failed to cause an increase in the volume of gastric juice secreted. This period varied from four and a half to five hours.

Collections were made from the pouches under control conditions and when the animals were receiving corticotrophin or corticoids. Four dogs were tested on each drug. The drugs, doses, and methods of administration were as follows:

(1) Corticotrophin Gel.—Twenty-five clinical units were injected intramuscularly once daily. It was anticipated that this would cause an endogenous secretion of cortisol equivalent to 100 mg. of cortisone.

(2) Cortisone Acetate (B.P.).—Fifty milligrams were injected intramuscularly twice daily (100 mg. per day). Previous reports had suggested that this dose would stimulate secretion of gastric acid. In some experiments, as noted later, smaller doses were used.

(3) Methyl Prednisolone (6-methyl-delta-1-hydrocortisone).—Four milligrams were given by mouth at 9.0 a.m. and 8 mg. at 5.0 p.m. (12 mg. per day). No parenteral preparation was available. This dose has

a glucocorticoid effect comparable with that of 100 mg. of cortisone.

(4) ALDOSTERONE.—dl - Aldosterone monoacetate, 0·2 mg., was injected intramuscularly once daily. This dose has a mineralocorticoid effect comparable with that of 100 mg. of cortisone.

All these substances were given for seven to 12 days. Longer periods of administration caused serious complications. An interval of at least three weeks was allowed to elapse between the stopping of one hormone and the starting of another, and collections were taken during this time to ensure that normal secretion had been re-established.

An estimate of the effect of corticoids on the cellular structure of the gastric mucosa was made as follows. Five control dogs were killed and their stomachs were removed immediately. From each stomach a strip of the gastric wall was taken at a point on the greater curvature 3 in. from the pylorus. This was fixed in 10% formol saline, embedded in wax, sectioned, and stained with haematoxylin and eosin. Six test dogs were given corticoids for 10 days and then killed and treated similarly. Three of

TABLE I

EFFECT OF CORTICOTROPHIN AND CORTICOIDS ON VOLUME OF GASTRIC JUICE

| | Mean Volume of Gastric Juice (ml./½ Hour) | | |
|---|---|---|---|
| | | Stimulated | |
| | Unstimulated | Histamine | Meat Extract |
| Control | 0·5 | 7·9 | 3·3 |
| Corticotrophin | | | |
| Mean difference* | + 0·5 | + 3·9 | + 3·3 |
| S.E. of difference | 0·05 | 1·5 | 0·5 |
| t (D. of F.) | 18·3 (3) | 3·2 (3) | 7·4 (2) |
| P | P < 0·001 | 0·05 > P > 0·02 | 0·02 > P > 0·01 |
| Cortisone | | | |
| Mean difference* | − 0·2 | + 3·2 | + 4·9 |
| S.E. of difference | 0·9 | 0·7 | 1·4 |
| t (D. of F.) | 0·03 (3) | 4·5 (3) | 3·5 (1) |
| P | 0·8 > P > 0·7 | 0·05 > P > 0·02 | 0·2 > P > 0·1 |
| Methyl prednisolone | | | |
| Mean difference* | + 0·6 | + 1·9 | + 4·2 |
| S.E. of difference | 0·5 | 1·4 | 1·3 |
| t (D. of F.) | 2·33 (3) | 1·4 (3) | 3·1 (3) |
| P | 0·2 > P > 0·1 | 0·3 > P > 0·2 | 0·1 > P > 0·05 |
| Aldosterone | | | |
| Mean difference* | + 0·5 | + 2·9 | + 3·7 |
| S.E. of difference | 0·2 | 0·9 | 0·4 |
| t (D. of F.) | 5·13 (3) | 3·2 (3) | 8·1 (2) |
| P | 0·02 > P > 0·01 | 0·05 > P > 0·02 | 0·02 > P > 0·01 |

The t test for paired data has been used for the statistical analysis in Tables I to VIII.
*Test values minus control values.

TABLE II

EFFECT OF CORTICOTROPHIN AND CORTICOIDS ON THE FREE HCl AND *p*H OF GASTRIC JUICE

| | Mean Free HCl (mEq./l.) | | | Mean *p*H | | |
|---|---|---|---|---|---|---|
| | Unstimulated | Histamine | Meat Extract | Unstimulated | Histamine | Meat Extract |
| Control | 0 | 98 | 69 | 5·8 | 1·4 | 1·7 |
| Corticotrophin | | | | | | |
| Mean difference* | + 24 | + 39 | + 58 | − 2·6 | − 0·3 | − 0·6 |
| S.E. of difference | 1·7 | 11·4 | 21·3 | 0·4 | 0·001 | 0·01 |
| t (D. of F.) | 14·5 (3) | 3·6 (3) | 2·7 (2) | 6·5 (3) | 3·4 (3) | 69 (2) |
| P | 0·01>P>0·001 | 0·05>P>0·02 | 0·2>P>0·1 | 0·01>P>0·001 | 0·05>P>0·02 | P<0·001 |
| Cortisone | | | | | | |
| Mean difference* | + 16 | + 37 | + 25 | − 2·5 | − 0·2 | − 0·6 |
| S.E. of difference | 5·6 | 9·5 | 13 | 0·5 | 0·1 | 0·1 |
| t (D. of F.) | 2·9 (3) | 3·9 (3) | 1·9 (1) | 4·7 (3) | 2·9 (3) | 11·4 (1) |
| P | 0·1>P>0·05 | 0·05>P>0·02 | 0·4>P>0·3 | 0·02>P>0·01 | 0·1>P>0·05 | 0·1>P>0·05 |
| Methyl prednisolone | | | | | | |
| Mean difference* | + 49 | + 22 | + 47 | − 3·6 | − 0·2 | − 0·5 |
| S.E. of difference | 9·2 | 12·5 | 20·1 | 0·5 | 0·001 | 0·003 |
| t (D. of F.) | 5·4 (3) | 1·7 (3) | 2·3 (3) | 7·5 (3) | 2·9 (3) | 16·4 (3) |
| P | 0·02>P>0·01 | 0·2>P>0·1 | 0·2>P>0·1 | 0·01>P>0·001 | 0·1>P>0·05 | P<0·001 |
| Aldosterone | | | | | | |
| Mean difference* | + 29 | + 39 | + 64 | − 2·9 | − 0·3 | − 0·6 |
| S.E. of difference | 7·5 | 10·9 | 24·1 | 0·4 | 0·004 | 0·01 |
| t (D. of F.) | 3·8 (3) | 3·6 (3) | 2·7 (2) | 6·4 (3) | 3·4 (3) | 69·2 (2) |
| P | 0·05>P>0·02 | 0·05>P>0·02 | 0·2>P>0·1 | 0·01>P>0·001 | 0·05>P>0·02 | P<0·001 |

*Test values minus control values.

these received cortisone and three methyl prednisolone in the doses described above. The sections were examined histologically and differential cell counts were made with the help of an eyepiece micrometer. Twenty squares (each 0·01 sq. mm. in area) were counted in each section, 10 at a standard distance (0·03-0·04 mm.) from the mucosal surface and 10 at a standard distance (0·02-0·03 mm.) from the muscularis mucosae.

## Results

VOLUME.—The unstimulated basal juice was affected very little. Corticotrophin and aldosterone, however, caused a slight but consistent reduction. The response to histamine and to meat extract was increased consistently. In a subsidiary experiment, cortisone, in a dose of 50 mg. per day, caused a three-fold increase in volume of the unstimulated juice in one of two dogs. Table I summarizes these results.

SECRETION OF ACID.—The *p*H was reduced and the concentration of free acid was increased consistently by corticotrophin and all the steroids (Table II). The most striking effect was seen in the basal unstimulated juice which was usually neutral (mean *p*H 5·8) under control conditions and highly acid (mean *p*H 2·9) during the administration of corticotrophin and all the steroids. The effects were not observed until these substances had been given for three to five days. In a subsidiary experiment this effect on basal juice was also produced by cortisone in a dose of 50 mg. per day; 25 mg. per day had a slight effect but 12·5 mg. had none.

MAXIMAL SECRETORY RESPONSE.—The maximal secretory response to histamine was tested in four dogs under control conditions and again when they were receiving cortisone. The pouches were usually secreting maximally between four and four and a half hours after the first injection of histamine. After this time the rate of secretion fell even with increasing doses. The results have been calculated in terms of

TABLE III

TOTAL VOLUME OF GASTRIC JUICE AND QUANTITY OF FREE HCl SECRETED IN RESPONSE TO INCREASING DOSES OF HISTAMINE

| Dog | No. of Tests | Control (mean) | No. of Tests | Cortisone (mean) | Difference | | |
|---|---|---|---|---|---|---|---|
| *Volume (ml.)* | | | | | | | |
| 159 | 1 | 122·6 | 1 | 138·3 | + 15·7 | + 13% | Mean + 59% |
| 196 | 1 | 126·2 | 1 | 218·3 | + 92·1 | + 73% | |
| 201 | 2 | 95·6 | 2 | 162·3 | + 66·7 | + 70% | |
| 202 | 2 | 121·3 | 3 | 220·4 | + 99·1 | + 82% | |
| Statistical analysis: | t = 3·6 | D.F. = 3 | 0·05 > P > 0·02 | | | | |
| *Free HCl (mEq.)* | | | | | | | |
| 159 | 1 | 16·4 | 1 | 21·3 | + 4·9 | + 30% | Mean + 81% |
| 196 | 1 | 15·7 | 1 | 30·4 | + 14·7 | + 94% | |
| 201 | 2 | 12·2 | 2 | 24·2 | + 12·0 | + 98% | |
| 202 | 2 | 15·6 | 3 | 31·8 | + 16·2 | + 104% | |
| Statistical analysis: | t = 4·74 | D.F. = 3 | 0·02 > P > 0·01 | | | | |

TABLE IV

VOLUME OF GASTRIC JUICE, CONCENTRATION OF FREE HCl, AND QUANTITY OF FREE HCl OBTAINED IN THE 15-MINUTE PERIOD OF MAXIMAL RESPONSE TO INCREASING DOSES OF HISTAMINE

| Dog | No. of Tests | Control (mean) | No. of Tests | Cortisone (mean) | Difference | | |
|---|---|---|---|---|---|---|---|
| *Volume (ml.)* | | | | | | | |
| 159 | 1 | 11·5 | 1 | 15·0 | + 3·5 | + 30% | Mean + 51% |
| 196 | 1 | 11·2 | 1 | 17·5 | + 6·3 | + 56% | |
| 201 | 2 | 8·8 | 2 | 14·0 | + 5·2 | + 59% | |
| 202 | 2 | 13·2 | 3 | 21·3 | + 8·1 | + 61% | |
| Statistical analysis: | t = 6·10 | D.F. = 3 | 0·01 > P > 0·001 | | | | |
| *Concentration of Free HCl (mEq./l.)* | | | | | | | |
| 159 | 1 | 160 | 1 | 174 | + 14 | + 9% | Mean + 9% |
| 196 | 1 | 162 | 1 | 172 | + 10 | + 6% | |
| 201 | 2 | 156 | 2 | 170 | + 14 | + 9% | |
| 202 | 2 | 152 | 3 | 169 | + 17 | + 11% | |
| Statistical analysis: | t = 9·55 | D.F. = 3 | 0·01 > P > 0·001 | | | | |
| *Free HCl (mEq.)* | | | | | | | |
| 159 | 1 | 1·8 | 1 | 2·6 | + 0·8 | + 44% | Mean + 49% |
| 196 | 1 | 1·8 | 1 | 2·5 | + 0·7 | + 39% | |
| 201 | 2 | 1·5 | 2 | 2·4 | + 0·9 | + 60% | |
| 202 | 2 | 1·9 | 3 | 2·9 | + 1·0 | + 53% | |
| Statistical analysis: | t = 13·2 | D.F. = 3 | P < 0·001 | | | | |

secretion during the four and a half-hour period (Table III). The total volume of juice secreted was increased greatly by cortisone in all the animals. The total amount of free HCl was about doubled in three of them and increased by one third in the fourth. The rate of secretion increased initially more rapidly when the dogs were receiving cortisone than it did during the control period. The maximum or "peak" rate was observed at about the same time in all the tests. The volume of juice, concentration of free HCl, and quantity of free HCl secreted during the 15-minute period of maximal response were increased appreciably by cortisone (Table IV).

SECRETION OF PEPSIN.—The secretion of pepsin was not affected much (Table V). If anything its concentration in the juice was reduced by all the substances and in the case of the basal secretion of dogs receiving methyl prednisolone the reduction was substantial.

TABLE V

EFFECT OF CORTICOTROPHIN AND CORTICOIDS ON PEPSIN IN GASTRIC JUICE

| | Mean Pepsin Concentration (Mett units) | | |
|---|---|---|---|
| | Unstimulated | Stimulated | |
| | | Histamine | Meat Extract |
| Control | 962 | 116 | 39·0 |
| Corticotrophin<br>Mean difference*<br>S.E. of difference<br>t (D. of F.)<br>P | − 14<br>108<br>0·1 (3)<br>P > 0·9 | − 22<br>22<br>0·02 (3)<br>P > 0·9 | + 4·0<br>8·1<br>0·36 (2)<br>0·8 > P > 0·7 |
| Cortisone<br>Mean difference*<br>S.E. of difference<br>t (D. of F.)<br>P | − 379<br>876<br>0·4 (3)<br>0·7 > P > 0·6 | − 51<br>25<br>2·0 (3)<br>0·2 > P > 0·1 | + 7·5<br>6·5<br>1·2 (1)<br>0·5 > P > 0·4 |
| Methyl prednisolone<br>Mean difference*<br>S.E. of difference<br>t (D. of F.)<br>P | − 1154<br>37<br>7·9 (3)<br>0·01 > P > 0·001 | − 61<br>34<br>1·7 (3)<br>0·2 > P > 0·1 | − 2·8<br>17·5<br>0·2 (3)<br>0·9 > P > 0·8 |
| Aldosterone<br>Mean difference*<br>S.E. of difference<br>t (D. of F.)<br>P | − 128<br>102<br>1·3 (3)<br>0·3 > P > 0·2 | − 22<br>32<br>0·7 (3)<br>0·6 > P > 0·5 | − 1·3<br>8·3<br>0·2 (2)<br>0·9 > P > 0·8 |

*Test values minus control values.

TABLE VI

EFFECT OF CORTICOTROPHIN AND CORTICOIDS ON VISCOSITY OF GASTRIC JUICE

| | Mean Viscosity (seconds) | | |
|---|---|---|---|
| | Unstimulated | Stimulated | |
| | | Histamine | Meat Extract |
| Control | 19·6 | 8·4 | 8·2 |
| Corticotrophin<br>Mean difference*<br>S.E. of difference<br>t (D. of F.)<br>P | − 7·5<br>3·5<br>2·1 (3)<br>0·2 > P > 0·1 | − 0·2<br>1·3<br>0·5 (3)<br>0·8 > P > 0·7 | 0<br>0·1<br>0 (2)<br>P > 0·9 |
| Cortisone<br>Mean difference*<br>S.E. of difference<br>t (D. of F.)<br>P | − 6·0<br>3·0<br>2·0 (3)<br>0·2 > P > 0·1 | 0<br>1<br>0 (3)<br>P > 0·9 | 0<br>0·4<br>0 (1)<br>P > 0·9 |
| Methyl prednisolone<br>Mean difference*<br>S.E. of difference<br>t (D. of F.)<br>P | − 3·0<br>4·2<br>0·7 (3)<br>0·6 > P > 0·5 | + 1·7<br>0·7<br>2·4 (3)<br>0·1 > P > 0·05 | + 2·0<br>0·6<br>3·6 (3)<br>0·05 > P > 0·02 |
| Aldosterone<br>Mean difference*<br>S.E. of difference<br>t (D. of F.)<br>P | − 7·1<br>3·8<br>1·9 (3)<br>0·2 > P > 0·1 | + 0·3<br>1·2<br>0·5 (3)<br>0·8 > P > 0·7 | + 0·5<br>0·4<br>0·4 (2)<br>0·3 > P > 0·2 |

SECRETION OF MUCUS.—The viscosity of the resting juice tended to be lower in the test periods than in the control ones, but the differences were not significant (Table VI). The protein content of the juice secreted in response to maximal histamine stimulation was measured in two dogs (Table VII). Cortisone caused a reduction of 25%.

TABLE VII

EFFECT OF CORTISONE ON PROTEIN CONTENT OF GASTRIC JUICE

| Dog | Control (mg./l.) | Cortisone (mg./l.) |
|---|---|---|
| 201 | 150 | 182 |
| 202 | 250 | 111<br>171<br>136 |
| Mean | 200 | 150 |

SECRETION OF ELECTROLYTES.—The concentration of sodium was reduced considerably and that of potassium (Table VIII) slightly by all the substances. The concentration of chloride was not affected.

CELLULAR STRUCTURE OF GASTRIC MUCOSA.—On naked-eye examination of the stomachs *post mortem* the mucosa of those dogs which had received corticoids appeared redder than those of the controls. Two of the dogs which had received cortisone had small petechial haemorrhages, but there was no obvious ulceration.

Microscopically no obvious lesions were present and the height of the mucosa and the number of mucosal folds were the same in the control as in the test groups.

The differential cell counts (Table IX) showed that the number of parietal cells was increased by about 50% and the number of peptic cells decreased by about 36% in the dogs which had received corticoids. In the control dogs there were more parietal cells than peptic cells in the superficial part of the mucosa (0·03-0·04 mm. from the surface) and more peptic than parietal cells in the deeper part. In the test dogs the parietal outnumbered the peptic cells in all parts of the mucosa.

TABLE VIII

EFFECT OF CORTICOTROPHIN AND CORTICOIDS ON CONCENTRATIONS OF SODIUM, POTASSIUM, AND CHLORIDE IN GASTRIC JUICE

| | Mean Sodium (mEq./l.) | | | Mean Potassium (mEq./l.) | | | Mean Chloride (mEq./l.) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Stimulated | | | Stimulated | | | Stimulated | |
| | Unstimulated | Histamine | Meat Extract | Unstimulated | Histamine | Meat Extract | Unstimulated | Histamine | Meat Extr |
| Control | 109 | 47 | 72 | 16·3 | 22·4 | 18·3 | 140 | 158 | 148 |
| Corticotrophin | | | | | | | | | |
| Mean difference* | − 82 | − 22 | − 28 | − 5·1 | − 1·7 | − 0·3 | + 5·0 | + 3·0 | + 5·0 |
| S.E. of difference | 5·5 | 2·0 | 2·5 | 5·0 | 1·9 | 1·4 | 4·0 | 1·5 | 6·4 |
| t (D. of F.) | 15·0 (3) | 4·5 (3) | 7·0 (2) | 2·6 (3) | 0·9 (3) | 2·8 (2) | 1·9 (3) | 1·9 (3) | 1·1 (2) |
| P | P<0·001 | 0·0>P>0·02 | 0·2>P>0·1 | 0·1>P>0·05 | 0·5>P>0·4 | 0·2>P>0·1 | 0·2>P>0·1 | 0·2>P>0·1 | 0·4>P>0·2 |
| Cortisone | | | | | | | | | |
| Mean difference* | − 40 | − 17 | − 31 | − 4·5 | − 2·5 | − 0·5 | − 3 | + 6 | + 5 |
| S.E. of difference | 16·5 | 2·0 | 5·5 | 5·7 | 3·4 | 4·1 | 2·4 | 0·5 | 2·0 |
| t (D. of F.) | 2·4 (3) | 2·9 (3) | 13·2 (1) | 2·3 (3) | 0·7 (3) | 1·0 (1) | 0·6 (3) | 1·5 (3) | 2·5 (2) |
| P | 0·1>P>0·05 | 0·1>P>0·05 | 0·05>P>0·02 | 0·2>P>0·1 | 0·6>P>0·5 | P = 0·5 | 0·6>P>0·5 | 0·3>P>0·2 | 0·3>P>0·2 |
| Methyl prednisolone | | | | | | | | | |
| Mean difference* | − 65 | − 30 | − 29 | − 1·2 | − 6·5 | − 1·8 | − 7 | − 2 | + 6 |
| S.E. of difference | 10·5 | 4·2 | 8·6 | 9·1 | 0·9 | 1·7 | 9·2 | 0·9 | 4·6 |
| t (D. of F.) | 6·2 (3) | 3·3 (3) | 3·2 (3) | 0·3 (3) | 7·5 (3) | 2·0 (3) | 0·9 (3) | 1·0 (3) | 1·4 (3) |
| P | 0·01>P>0·001 | 0·05>P>0·02 | 0·1>P>0·05 | 0·8>P>0·7 | 0·01>P>0·001 | 0·2>P>0·1 | 0·5>P>0·4 | 0·4>P>0·3 | 0·4>P>0·2 |
| Aldosterone | | | | | | | | | |
| Mean difference* | − 50 | − 11 | − 30 | − 6·0 | − 5·5 | − 4·0 | + 6 | + 2 | + 7 |
| S.E. of difference | 5·4 | 3·0 | 1·8 | 6·2 | 1·5 | 2·7 | 8·5 | 1·5 | 5·0 |
| t (D. of F.) | 9·3 (3) | 1·7 (3) | 3·5 (2) | 2·0 (3) | 3·7 (3) | 2·6 (2) | 3·5 (3) | 0·8 (3) | 1·4 (3) |
| P | 0·01>P>0·001 | 0·2>P>0·1 | 0·1>P>0·05 | 0·2>P>0·1 | 0·05>P>0·02 | 0·2>P>0·1 | 0·05>P>0·02 | 0·5>P>0·4 | 0·3>P>0·2 |

*Test values minus control values.

TABLE IX

EFFECTS OF CORTISONE AND OF METHYL PREDNISOLONE ON NUMBERS OF PARIETAL AND PEPTIC CELLS IN GASTRIC MUCOSA

| | Parietal Cells | | Peptic Cells | |
|---|---|---|---|---|
| Controls | | 1,040* (S.D.126)‡ | | 1,060 (S.D.93)† |
| Cortisone | 1,580 | 1,575 (S.D.156)† | 660 | 675 (S.D.110)‡ |
| Methyl prednisolone | 1,570 | | 690 | |

*All figures are means and refer to cells per sq. mm. of field.
†Comparison of the two means, t = 5·90 D.F. = 9, P<0·001.
‡Comparison of the two means, t = 6·42 D.F. = 9, P<0·001.

## Discussion

These results confirm that the secretions of the adrenal cortex, in pharmacological doses, exert an influence on gastric secretion.

Corticotrophin and cortisone stimulate the secretion of acid in the basal juice and augment its secretion in response to histamine and antral stimulation. Moreover, cortisone increases the maximal secretory response to histamine. All but one of these observations (the effect on the basal juice) can be explained by the increase in number of the parietal cells in the gastric mucosa which our preliminary studies have shown. Moreover, the delay of three to four days before any effect is observed may well reflect the time required for the cells to multiply. A simple increase in the number of acid-secreting cells, however, does not explain the observation that the basal juice regularly contains free acid under the influence of corticotrophin and cortisone while it rarely does so under control conditions. It must be concluded that these substances stimulate the parietal cells to secrete as well as to divide.

Two sets of observations indicate that hydrogen ion secretion is stimulated directly and that the effect is not dependent on the behaviour of other electrolyte ions. The first is the finding that the concentrations of sodium and potassium are reduced and that that of chloride is unchanged. If these ions were affected primarily, as they are in the kidney and in the sweat glands, the sodium and chloride would be reduced and the potassium increased. The second is the finding that methyl prednisolone (a relatively pure glucocorticoid) influences the secretion of acid and of electrolytes in the same way as cortisone does. If the primary action were on the metallic ions, methyl prednisolone would be expected to have a lesser effect on them. It is likely that the reduction in sodium and potassium ions is related to the increase in hydrogen ions in the gastric juice.

The stimulatory effect is still unexplained. The fact that aldosterone (of which the glucocorticoid action is minimal) and methyl prednisolone (of which the mineralocorticoid action is minimal) have the same influence on gastric secretion as cortisone does indicates that the effect is not dependent on their main metabolic properties.

The method which was used for the estimation of pepsin is not a very accurate one and little weight can be attached to the results. However, the tendency for its concentration to be reduced is consistent with the apparent reduction in the number of peptic cells observed histologically.

The effects of corticoids on the secretion of mucus still await full investigation. Our limited results suggest that the secretion is reduced. It may be, as has been suggested (Hirschowitz *et al.*, 1955), that the lowering of the defensive mucous barrier is one factor in the pathogenesis of steroid ulceration. Another, clearly, is the increase of acid secretion, particularly in the empty stomach.

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# SEROTONIN, BANANAS, AND DIARRHOEA

BY

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From previous studies on serotonin it seemed possible that it might play a major rôle in determining the rhythm of the bowel in man. This hypothesis was tested, with negative results, by observing the effect of giving bananas, a rich natural source of serotonin, to normal subjects and by measuring the excretion of 5-hydroxyindolacetic acid in patients with diarrhoea.

"Is 5-hydroxytryptamine (5-H.T.) Nature's remedy for constipation?" This speculation (Collier, 1958) about a possible rôle for 5-H.T. was prompted by the following observations: it is present in the intestinal mucosa in higher concentration than in any other tissue of the body; it causes isolated pieces of intestine to contract; and when given to mice by injection (Erspamer, 1952) or by mouth it increases the amount of faeces passed, "as a much larger dose of senna does" (Collier, 1958). Bülbring and Lin (1958) have also recently shown that 5-H.T. stimulates peristalsis when introduced into the lumen of the isolated guinea-pig intestine. These observations lend some support to the view that 5-H.T. may be concerned in the regulation of bowel function in some animals, and, by inference, in man, especially as diarrhoea is a prominent symptom of the carcinoid syndrome. We have, therefore, tried to obtain further evidence about the relationship between 5-H.T. and bowel function in man in two separate studies.

As very little is known about the fate of 5-H.T. or its effect on intestinal motility when given by mouth, we observed the effects of feeding large amounts of it in the form of bananas to a group of normal subjects and measured its excretion in the urine as 5-hydroxyindoleacetic acid (5-H.I.A.A.). Anderson, Ziegler, and Doeden (1958) noted that monkeys excreted much more 5-H.I.A.A. when bananas were added to their diet, and Waalkes, Sjoerdsma, Creveling, Weissbach, and Udenfriend (1958) showed that this was because bananas contain large amounts of serotonin. This surprising finding was of further interest because bananas have enjoyed a traditional reputation in the treatment of coeliac disease and other bowel disorders. In our second study we measured the excretion of 5-H.I.A.A. in patients suffering from chronic diarrhoea and steatorrhoea, since it seemed possible that overproduction of 5-H.T. might be concerned in the aetiology of this obscure group of diseases.

*In receipt of grants from the Medical Research Council.

## Method

Specimens of urine were collected over 24-hour periods, and the 5-H.I.A.A. was estimated by the method of Macfarlane, Dalgliesh, Dutton, Lennox, Nyhus, and Smith (1956) which is a modification of the method of Udenfriend, Titus, and Weissbach (1955). Chromatography was not performed as it has been shown that the colour reaction is produced mainly by 5-H.I.A.A. The recovery of known amounts of 5-H.I.A.A. added to urine averaged 88% over a range of concentration of 8 to 20 $\mu$g./ml.

## Results

The daily excretion of 5-H.I.A.A. in 19 normal subjects ranged from 1·9 to 7·6 mg. with a mean of 3·9 mg. The individual values are shown in Fig. 1. Unlike a number of physiological substances, there does not appear to be any diurnal variation in the excretion of 5-H.I.A.A. (Table I). Our results are rather lower than those of Macfarlane *et al.* (1956) (range 3·2 to 13·7 mg. per day) but correspond closely to the normal values quoted by Udenfriend and other authors. In two patients with carcinoid tumours, subsequently confirmed at necropsy, the mean excretion of 5-H.I.A.A. was 51 mg. and 81 mg. per 24 hours respectively.

Effects of Eating Bananas.—Six normal subjects collected urine for 24 hours in three separate eight-hourly periods. On the following day the same procedure was observed but during the first three hours each subject ate 12 bananas, most of which were eaten in the first hour. A marked and

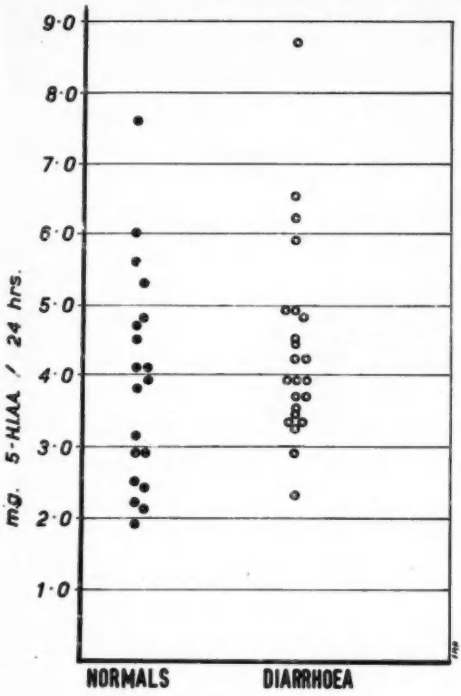


FIG. 1.—*Daily excretion of 5-H.I.A.A. in 19 normal subjects.*

rapid rise in 5-H.I.A.A. excretion was observed on the day the bananas were eaten (Table I), the mean increase being 22·3 mg. Waalkes *et al.* (1958) found that the serotonin content of banana pulp ranged from 8 to 50 μg./g. and averaged 28 μg./g., the average weight of pulp per banana being 130 g. Although our bananas were large by British standards, the pulp weighed only about 100 g., and their serotonin content was also probably lower than that of the American bananas since West (1958), working in London, obtained values of 19·0 to 25·0 μg. of 5-H.T. per g. of pulp. Assuming that the amount of serotonin in each banana was between 1·9 and 2·5 mg., each of our subjects ingested between 23 and 30 mg. of 5-H.T., and excreted between 75% and 100% of it as 5-H.I.A.A. in 24 hours (the ratio of the molecular weights of 5-H.T. and 5-H.I.A.A. is 0·92).

The rate of elimination from the body was rapid, the greater proportion being excreted in the first eight hours, when the level of urinary 5-H.I.A.A. was well into the range found in patients with carcinoid tumours. The mean rate of excretion in the first eight-hour period after ingestion of bananas was 2·3 mg. per hour, compared with 2·1 mg. and 3·4 mg. per hour respectively in our two patients with carcinoid tumours.

The ingestion of as few as three bananas was sufficient to raise the excretion of 5-H.I.A.A. above the normal limit in our subjects, the excretion in the first eight hours averaging 4·9 mg. more than in the corresponding control period.

None of the subjects developed symptoms which could not be attributed to increased bulk alone, even though four of them ate 12 bananas daily for six days in addition to their normal diet, their excretion of 5-H.I.A.A. averaging 28·7 mg. on the first day and 34·0 mg. on the sixth. Most of them experienced a sensation of satiety from overeating, but none of them complained of diarrhoea, urgency, colic, or borborygmi.

URINARY 5-H.I.A.A. IN CHRONIC DIARRHOEA.—The excretion of 5-H.I.A.A. was measured in 20 patients suffering from chronic diarrhoea of unknown aetiology and without steatorrhoea. Eleven of these complained of persistent early morning diarrhoea, and the remaining nine patients had frequent attacks of profuse diarrhoea alternating with periods of complete or partial remission. Two patients with ulcerative colitis and one with Crohn's disease were also studied. The mean excretion of 5-H.I.A.A. in this group of patients was 4·3 mg. per day, and Fig. 1 shows that the scatter of the individual values is essentially the same as in normal subjects.

TABLE I

EFFECT OF EATING 12 BANANAS ON URINARY EXCRETION OF 5-H.I.A.A. (MG.)

| Subject | Control Day | | | | Experimental Day | | | |
|---|---|---|---|---|---|---|---|---|
| | 3-11 p.m. | 11 p.m.-7 a.m. | 7 a.m.-3 p.m. | Total | 3-11 p.m. | 11 p.m.-7 a.m. | 7 a.m.-3 p.m. | Total |
| M.F. | 2·0 | 2·1 | 1·2 | 5·3 | 22·4 | 7·9 | 1·2 | 31.5 |
| E.C. | 1·3 | 1·3 | 1·5 | 4·1 | 8·4 | 6·5 | 5·1 | 20·0 |
| E.N.R. | 1·4 | 1·4 | 1·1 | 3·9 | 19·8 | 4·0 | 2·0 | 25·8 |
| A.M.C. | 0·8 | 0·8 | 0·8 | 2·4 | 16·5 | 3·2 | 1·2 | 20·9 |
| P.B.W. | 0·9 | 1·0 | 1·0 | 2·9 | 25·9 | 1·9 | 0·5 | 28·3 |
| A.C. | 1·4 | 0·6 | 2·8 | 4·8 | 19·3 | 9·0 | 2·4 | 30·7 |
| Mean | 1·3 | 1·2 | 1·4 | 3·9 | 18·7 | 5·4 | 2·1 | 26·2 |

URINARY 5-H.I.A.A. in STEATORRHOEA.—This group consisted of nine patients with idiopathic steatorrhoea (Table II), and eight in whom the steatorrhoea was secondary to one of the diseases listed in Table III. One of the patients with the Zollinger-Ellison syndrome has been described elsewhere by Summerskill (1959). Both the others had pancreatic tumours. The diagnosis of idiopathic steatorrhoea was made only after intensive investigations had failed to reveal any cause for the condition.

TABLE II

URINARY EXCRETION OF 5-H.I.A.A. (MG. per 24 HR.) IN PATIENTS WITH IDIOPATHIC STEATORRHOEA

| Patient No. | In Relapse | Treated with Gluten-free Diet |
|---|---|---|
| 1 | 3·9 2·7 4·0 | — |
| 2 | 4·0 | — |
| 3 | 4·0 4·7 | — |
| 4 | 6·4 | — |
| 5 | 7·3 | — |
| 6 | 9·1 4·1 8·4 | — |
| 7 | 3·1 4·8 | 3·1 5·8 |
| 8 | 2·1 | 1·4 1·3 1·3 |
| 9 | — | 2·9 |

TABLE III

URINARY EXCRETION OF 5-H.I.A.A. (MG. PER 24 HR.) IN PATIENTS WITH SECONDARY STEATORRHOEA

| | |
|---|---|
| *Zollinger-Ellison Syndrome* | |
| 1 | 4·1 |
| 2 | 1·7 1·9 |
| 3 | 15·9 4·3 |
| *Pancreatic Steatorrhoea* | |
| 1 | 7·3 |
| 2 | 5·1 |
| *Post-gastrectomy Steatorrhoea* | |
| 1 | 3·7 |
| 2 | 4·1 |
| *Ileo-colitis* | 7·4 3·6 11·1 |

In the patients with idiopathic steatorrhoea the urinary excretion of 5-H.I.A.A. ranged from 1·3 to 9·1 mg. per day. Table II shows the individual values in six patients in relapse, in one patient who was in a remission induced by a gluten-free diet, and in two patients before and after treatment with gluten-free diets. Normal values were obtained in all these patients, whether in relapse or in remission, except that two out of three estimations in one patient were just outside our normal range though within the commonly accepted range of 2 to 10 mg. per day (Pernow, 1958). In the patients with secondary steatorrhoea (Table III) the urinary levels were within the normal range with two exceptions: in one of the patients with the Zollinger-Ellison syndrome, one of the two estimations was well above the normal range; and one out of three estimations in the patient with ileocolitis was slightly elevated.

## DISCUSSION

Variations in diet, including major variations in the tryptophan content, are said to have little or no effect on the urinary 5-H.I.A.A. (Pernow, 1958). The excretion of this substance is regarded as the best index of the total production of 5-H.T. in the body, and is used as a specific test in the diagnosis of carcinoid tumours. It is therefore important to realize that the ingestion of a few bananas will raise the urinary 5-H.I.A.A. above the normal range because of their large content of serotonin. Of this, a high proportion, possibly as much as 100%, is rapidly excreted as 5-H.I.A.A. in normal individuals, and this might prove useful as a test of intestinal absorption. There is no satisfactory method of measuring the absorption of nitrogenous substances (Rowlands, 1959), but the oral administration of known amounts of serotonin and subsequent estimation of urinary 5-H.I.A.A. is a simple procedure which would appear to be worthy of further study in this connexion.

None of the subjects who ate bananas suffered from diarrhoea or any other abdominal symptoms although some of them consumed about 30 mg. of serotonin daily for a week, and their urinary 5-H.I.A.A. was elevated into the range commonly regarded as diagnostic of carcinoid tumour. Hendrix, Atkinson, Clifton, and Ingelfinger (1957) found that the instillation of up to 30 mg. of 5-H.T. into the lumen of the jejunum had no effect on intestinal motility as recorded by a balloon in normal subjects. These findings in man are in marked contrast to the effect of oral 5-H.T. on the intestine in animals (Collier, 1958), and also to Bülbring and Lin's (1958) observation that peristalsis was stimulated when 5-H.T. was introduced into the lumen of isolated guinea-pig ileum. It may be that species differences are important since Bülbring and Lin noted that the stimulating effect of intraluminal 5-H.T. developed more slowly and was less marked and more transient in rabbit jejunum than in guinea-pig ileum.

However, it has been shown experimentally in man that the intravenous injection of 5-H.T. usually stimulates intestinal motility (Hendrix *et al.*, 1957), and it is commonly believed that it is the overproduction of 5-H.T. which accounts for the diarrhoea in the carcinoid syndrome. It therefore seemed possible that it might also be a factor in the aetiology of the chronic diarrhoeas, but the production of 5-H.T. in our patients was within normal limits, as judged by their excretion of 5-H.I.A.A. Kowlessar, Williams, Law, and Sleisenger (1958) also found normal values in patients with diarrhoea without steatorrhoea. In patients with "symptomatic non-tropical sprue", however, these authors found that

the urinary excretion was high but it returned to normal levels when the symptoms had been controlled by a gluten-free diet. Although the majority of our patients with idiopathic steatorrhoea were either untreated or in relapse, only one of them showed a raised excretion of 5-H.I.A.A. and this was so small as to be of doubtful significance. There was no change in the urinary 5-H.I.A.A. of two patients who were studied before and after treatment with gluten-free diets. Krikler (1958) also reported a case of idiopathic steatorrhoea in which the excretion of 5-H.I.A.A. was normal. Haverback and Davidson (1958) made repeated measurements on two patients with non-tropical sprue and found that some of the 5-H.I.A.A. values "appeared to be border-line elevations". The 5-H.I.A.A. values were also normal in our patients with secondary steatorrhoea, with the exception of one of the patients with the Zollinger-Ellison syndrome associated with a malignant pancreatic tumour. The significance of the high value obtained in this patient is not apparent.

Although 5-H.T. is probably concerned in the control of intestinal motility, its precise role in normal intestinal physiology is speculative, and we have not found any evidence that it plays an important part in the aetiology of disorders of bowel function in man. Even in the carcinoid syndrome the correlation between 5-H.T. production and the occurrence of diarrhoea is poor; and a significant number of the patients never suffer from diarrhoea throughout their illness, *e.g.*, 15 out of 79 patients with malignant carcinoids reviewed by Thorson (1958). Thus, while it is reasonable to suppose that the overproduction of 5-H.T. may be a cause of the diarrhoea, it seems likely that the mechanical effect of the tumour is also a factor since it is located in the intestine in the majority of the patients.


## Summary

The daily ingestion of large amounts of serotonin in bananas did not affect bowel function in man, in contrast to the effect of oral and intraluminal 5-H.T. in animals.

A high percentage of the 5-H.T. content of the bananas was rapidly excreted as 5-H.I.A.A. in the urine; this might prove useful as a test of the intestinal absorption of a nitrogenous substance. The ingestion of three bananas was sufficient to raise the urinary 5-H.I.A.A. above the normal range.

There was no evidence of overproduction of 5-H.T. in patients with chronic diarrhoea of unknown aetiology or in idiopathic steatorrhoea. The excretion of 5-H.I.A.A. was also normal in secondary steatorrhoea, except in one out of three patients with the Zollinger-Ellison syndrome.


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# COELIAC DISEASE

## HISTOPATHOLOGICAL FINDINGS IN THE SMALL INTESTINAL MUCOSA STUDIED BY A PERORAL BIOPSY TECHNIQUE

BY

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Villous atrophy, changes in the surface epithelium, mucosal thickening, and glandular hypertrophy were a feature of all the mucosal biopsies from the small intestine obtained from eight coeliac children. No histological differences were observed between the children previously treated with intermittent gluten-free diets and the untreated children. Serial biopsy studies were carried out on one coeliac child before and after treatment with a gluten-free diet over a period of two years. On the whole they confirmed the irreversible nature of the observed histopathological changes but minor improvements could not be excluded. Mucosal abnormalities in coeliac disease are the same as in adult idiopathic steatorrhoea, where they are observed in patients with or without a response to a gluten-free diet. It is concluded that the elimination of gluten from the diet has little if any influence on the histopathological abnormalities observed in coeliac disease.

The clinical picture of coeliac disease was well described by Samuel Gee as long ago as 1888. He emphasized the passage of loose, bulky, pale, and offensive stools as the first and foremost sign of the disease, accompanied by anaemia, muscular atony, wasting, and stunted growth.

The aetiology of coeliac disease has, however, remained obscure. An anatomical lesion of the small intestine had never been demonstrated until the first report by Sakula and Shiner (1957) in which they described villous atrophy of the intestinal mucosa of the smaller intestine obtained by peroral biopsy technique from an untreated coeliac child. This work has now been extended to embrace seven more coeliac children who are the subjects of this report. In addition, repeat biopsies, over a period of two years while the patient was on a gluten-free diet, were performed on the child originally reported by Sakula and Shiner.

### METHOD

The child's intestinal biopsy tube (Fig. 1) is a modification of the adult suction biopsy tube (Shiner, 1956). It is of sufficiently small calibre to be used for intubating children of the age of 1 year. From half to one hour is required to take the biopsy.

The child is not usually sedated, but if necessary a mixture of pethidine, mg. 100, chlorpromazine, mg. 50, and promethazine, mg. 50, per 100 lb. of body weight may be administered intramuscularly. He should be fasting and the throat may be anaesthetized with a ½-1% amethocaine gargle. The tube is introduced in the left lateral position and its progress through the stomach and duodenum is followed fluoroscopically. The biopsy specimen is preferably taken from the first part of the jejunum but occasionally the head end of the tube will not travel further than the second or third part of the duodenum when the specimen is taken from these sites. A high negative pressure of 10 to 20 in. of mercury is necessary for adequate specimens to be sucked into the aperture. Several biopsy specimens can be obtained at any single intubation by varying the position of the tube. Once specimens are taken, the tube should be rapidly withdrawn and the specimens immediately fixed in 10% formol saline to avoid autolysis.

The method described has proved safe and no complications have occurred in the 18 children subjected to it. But it was not possible to obtain adequate specimens or to pass the tube beyond the pylorus in eight of these children.

### MATERIAL

Of the 10 children in whom adequate mucosal specimens were obtained, eight had coeliac disease, one juvenile pernicious anaemia, and one idiopathic hypoproteinaemia associated with steatorrhoea.

The diagnostic criteria of coeliac disease, namely diarrhoea, steatorrhoea, anaemia, and muscular atony in a stunted, underweight child, were strictly adhered to by their physicians in charge when the patients first came under observation.

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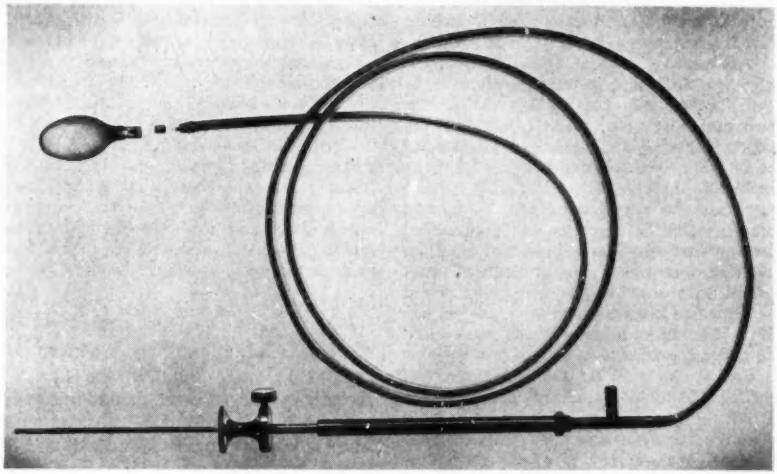

FIG. 1.—*The child's small intestinal biopsy tube.*

TABLE I

CLINICAL SUMMARY OF SERIES OF EIGHT COELIAC CHILDREN

| No. | Name | Age (yr.) | Sex | Height (in.) | Weight (lb.) | Diarrhoea | Abdominal Distension | Steatorrhoea (Faecal Fats) | Haemoglobin (%) | Glucose Tolerance Curve |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | G.C. | 10 | Male | 48¾ | 24 | No | No | 7·7 g./day | 98 | Normal |
| 2 | D.L. | 9 | Female | 43¾ | 38·8 | Yes | Yes | 91·5% absorption | 42 | Flat |
| 3 | P.K. | 2½ | Male | 30½ | 22·3 | Yes | Yes | 87% absorption | 86 | Flat |
| 4 | J.B. | 15 | Female | 57 | 81 | No | No | — | 52 | Normal |
| 5 | L.P. | 4½ | Female | 40 | 32 | Yes | Yes | 86% absorption | 62 | — |
| 6 | A.R. | 13½ | Male | 52½ | 60·7 | Yes | No | 58% absorption | 54* | Flat |
| 7 | J.N. | 2½ | Female | 34½ | 24·1 | Yes | Yes | 13 g./day | 80 | —† |
| 8 | M.R. | 7¾ | Male | 41¾ | 32 | Yes | Yes | 48% absorption | 74 | Flat |

* = macrocytic anaemia † = xylose excretion low

TABLE II

AGES AT ONSET AND DIAGNOSIS AND TREATMENT IN EIGHT COELIAC CHILDREN

| Case No. | Name and Age (yr.) | Age at Onset of Symptoms (yr.) | Age at Diagnosis (yr.) | Previous Treatment | Treatment at Time of Biopsy | Clinical Progress |
|---|---|---|---|---|---|---|
| 1 | G.C. (10) | Not known | 6¾ | Gluten-free diet for 4 years | No treatment for past 4 months | No gain in weight or increase in height during the past 4 months |
| 2 | D.L. (9) | 2 | 3 | Nil | No treatment | Good progress on gluten-free diet |
| 3 | P.K. (2½) | 1 | 2½ | Nil | On gluten-free diet for 3 days before biopsy | Under investigation |
| 4 | J.B. (15) | 1 | 1½ | Starch-free diet, then gluten-free diet for 2 years from age 11. Repeated blood transfusions | No treatment for 2 years before biopsy | Under investigation |
| 5 | L.P. (4½) | 3½ | 4½ | Nil | No treatment | Good progress on gluten-free diet |
| 6 | A.R. (13½) | 6 months | 6 | Gluten-free diet at intervals from age 8 onwards | No treatment for 4 months before biopsy | Under investigation |
| 7 | J.N. (2½) | 1½ | 2½ | Nil | On gluten-free diet for 12 days before biopsy | Under investigation |
| 8 | M.R. (7¾) | Not known | 5½ | Nil | No treatment before first biopsy<br>Five weeks on gluten-free diet before second biopsy<br>One year, five months on gluten-free diet before third biopsy<br>Two years, one month on gluten-fee diet before fourth biopsy | Good progress on gluten-free diet |

The coeliac children (Table I) comprised four boys and four girls. Their ages ranged from 2 years 3 months to 15 years. All were in hospital at the time of the present investigation and were in relapse, clinically or biochemically. Their heights and weights were below normal for their respective ages. Cases 2, 3, 5, 7, and 8 were previously undiagnosed and either had not received any treatment or had started a gluten-free diet for up to three weeks before biopsy (Table II). In Cases 1, 4, and 6 the diagnosis had been made at an earlier age. Case 1 had been on a gluten-free diet for four years, but had received a normal diet for the past four months. Faecal fat estimations showed a return of steatorrhoea. Case 4 had been treated with a starch-free diet and later a gluten-free diet but had been on a normal diet for the past four years. The present admission was necessitated by severe iron deficiency anaemia. Case 6 had been on a gluten-free diet at intervals for five years but had received a normal diet for four months before biopsy. He relapsed both clinically and biochemically with steatorrhoea and macrocytic anaemia. Case 8 was followed up for two years after beginning a gluten-free diet. While on this diet his height increased from 41¾ to 48¼ in. and his weight from 32 to 51 lb. Faecal fats fell from 26 to 4 g. per 24 hours.

The diagnosis of juvenile pernicious anaemia in one child was supported by vitamin $B_{12}$ absorption studies. Idiopathic hypoproteinaemia was diagnosed in the other child by studies with labelled serum albumin.

The biopsy specimens obtained from each of these children were examined. They varied in number from one to 10 and included full-thickness mucosa, muscularis mucosae, and sometimes a small amount of submucosa. They were more or less fragmented. The shape of the villi, the surface epithelium with nuclei, the mucosal thickness, the number of glands of Lieberkühn, the appearances of the glandular cells, and the amount of inflammatory reaction were examined in detail. Treatment, if any, with a gluten-free diet was related to the time of biopsy (Table II).

## Results

Normal Small Intestinal Mucosa.—This (Figs. 2a and 2b) was found in the two children with juvenile pernicious anaemia and idiopathic hypoproteinaemia. In appearance it was comparable to adult small intestinal mucosa (Doniach and Shiner, 1957; Shiner and Doniach, 1959). The villi were long, slender processes covered by regular, tall columnar epithelium containing basally situated, elongated nuclei. A faint basement membrane could be identified. The lamina propria contained relatively

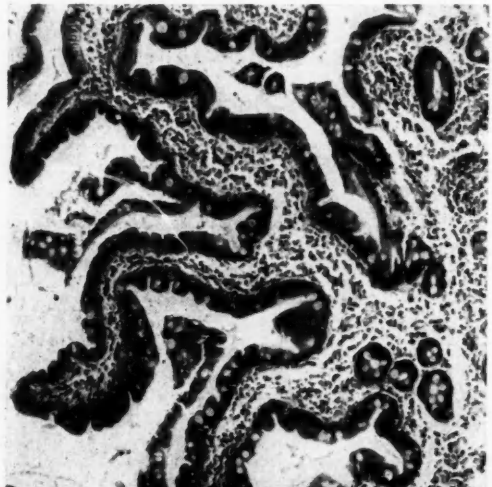

Fig. 2a.—*Biopsy of normal mucosa from patient with idiopathic hypoproteinaemia, showing villi and part of mucosa. Haematoxylin and eosin × 100.*

Fig. 2b.—*High-power view of villus from same biopsy. Haematoxylin and eosin × 370.*

TABLE I

HISTOLOGICAL FINDINGS IN EIGHT CASES OF COELIAC DISEASE

| Histological Details | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Site of biopsy | Duodeno-jejunal junction | Low duodenal | Duodeno-jejunal junction | Jejunum | Jejunum |
| No. of specimens | 3 | 3 | 4 | 5 | 8 |
| Villi | Absent | Absent | Absent | Absent | Absent |
| Surface epithelium | Reduced in height | Not well preserved | Reduced in height | Reduced in height | Reduced in height |
| Nuclei of surface epithelium | Irregular | — | Irregular, large, pale | Irregular, large, pale | Irregular, large, pale |
| Mucosal thickness | Increased | Increased | Increased | Increased | Increased |
| No. of glands of Lieberkühn | More numerous | More numerous | More numerous | More numerous | More numerous |
| Glandular cells | Normal | Normal | Normal | Normal | Normal |
| Interstitial cell infiltration | Increased, chronic type | Not excessive | Not excessive | Increased chronic type | Not excessive |

| Histological Details | Case 6 | Case 7 | Case 8 | | | |
|---|---|---|---|---|---|---|
| | | | First Biopsy | Second Biopsy | Third Biopsy | Fourth Biopsy |
| Site of biopsy | Low duodenal | Jejunum | Duodenum | Duodenum | Duodenum | Duodenum |
| No. of specimens | 1 | 6 | 4 | 10 | 4 | 3 |
| Villi | Almost absent, few short and broad villi | Absent | Broad, flat, or absent | Short, broad, or slender | Short and more slender | Short and broad or slender |
| Surface epithelium | Reduced in height | Reduced in height | Reduced | Reduced | Reduced | Reduced in height |
| Nuclei of surface epithelium | Irregular | Irregular, large, pale | Irregular | Irregular | Irregular | Irregular |
| Mucosal thickness | Increased | Increased | Increased | Increased | Less increased | Less increased |
| No. of glands of Lieberkühn | More numerous | More numerous | More numerous | More numerous | Less numerous | Less numerous |
| Glandular cells | Normal | Normal | Normal | Normal | Normal | Normal |
| Interstitial cell infiltration | Not excessive | Some increase, chronic type | No excess | No excess | No excess | No excess |

few glands of Lieberkühn and inflammatory cells were moderate in number, consisting mainly of lymphocytes and plasma cells. Mitosis was observed in the glandular cells but not in the villous cells. The ratio between lamina propria and villi was similar to that found in adults, the villi being about two-and-a-half times the height of the glandular layer.

THE MUCOSA IN COELIAC DISEASE.—Normal villi were not seen in any biopsy specimens from the eight children with coeliac disease (Table III). Surface appearances were either flat or showed occasional broad and short villi (Figs. 3a and 3b). The surface epithelium stained poorly, the cells were reduced to low columnar or cuboidal epithelium with their nuclei arranged in a disorderly pattern within the cells. Many of these nuclei, instead of being elongated and darkly staining, were pale and large. The basement membrane appeared interrupted in places or could not be seen at all. The mucosal thickness was invariably increased and the glands of Lieberkühn appeared more numerous than normal. An increase in inflammatory cells was noted in only three biopsies.

The first, pre-treatment biopsy, of Case 8 showed broad, flat villi with abnormal surface epithelium (Figs. 4a and b). The mucosal thickness was increased and the glands of Lieberkühn appeared more numerous than normal. The first repeat biopsy (Fig. 5) five weeks after the beginning of a gluten-free diet showed a similar picture but a few more slender though short villi could be identified. The surface cells showed no improvement. Three of the four specimens obtained at the second repeat biopsy 17 months later (Figs. 6a and b), while the child was still on a gluten-free diet, showed more attempts at villous formation. Though the villi still appeared rather short they were more slender and the normal indentations at the sides of these villi were noted. More crypts opening into the surface were seen. Though the surface epithelium showed little improvement at the tips and sides of the villi, it appeared more normal at the base of the budding villi and in the crypts. The third repeat biopsy showed a similar picture to the previous one. A few short but slender villi (Fig. 7a) were again noted but broad and short villi or a completely flat surface were also present (Fig. 7b). No further change in the surface epithelium was seen. The mucosal thickness was much increased in the region of overlying broad villi but it was less thick in the region of more normal villi. The glands of Lieberkühn appeared slightly less numerous.

## DISCUSSION

From the study of the small intestinal mucosa in adults in a wide variety of diseases affecting the alimentary tract it was observed that mucosal

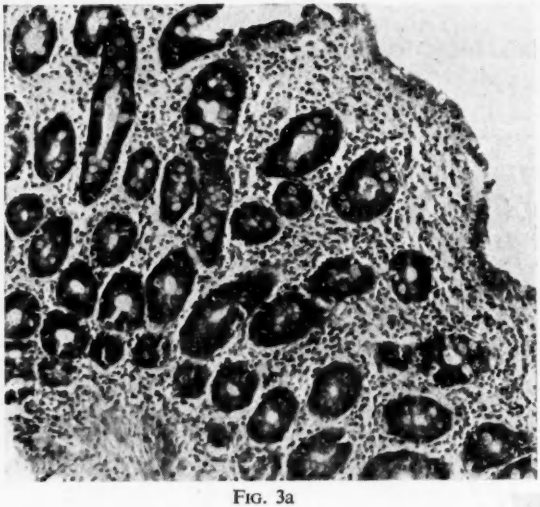

FIG. 3a

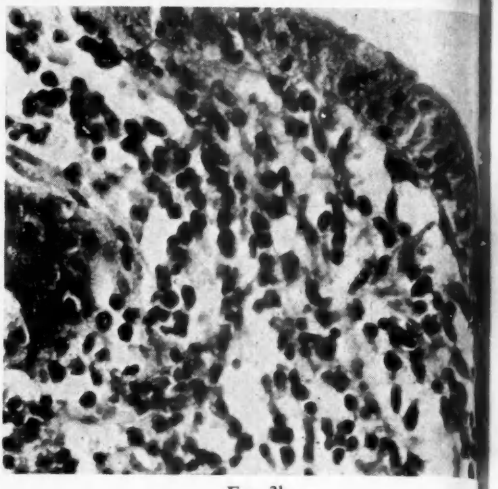

FIG. 3b

FIG. 4a

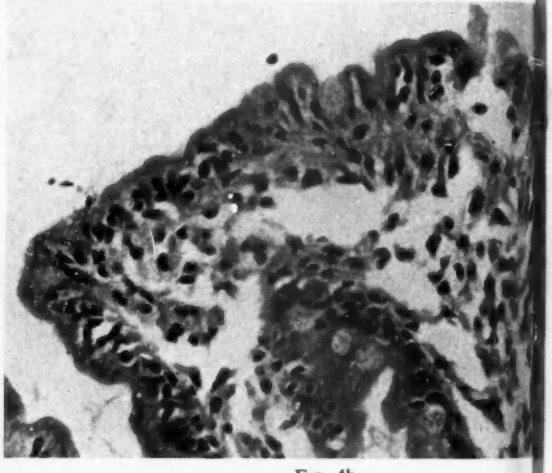

FIG. 4b

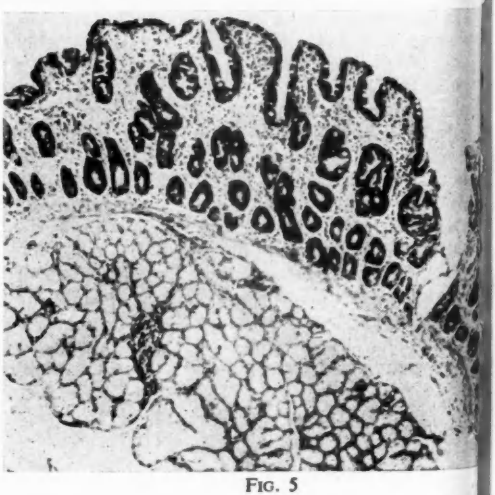

FIG. 5

FIG. 3a.—*Biopsy from coeliac patient P.K. aged 2 years 3 months, showing complete absence of villi. Haematoxylin and eosin × 100.*

FIG. 3b.—*High-power view of surface epithelium from same biopsy. Haematoxylin and eosin × 370.*

FIG. 4a.—*Original, pre-treatment biopsy from patient M.R. Haematoxylin and eosin × 50.*

FIG. 4b.—*High-power view of short villus from same biopsy. Haematoxylin and eosin × 370.*

FIG. 5.—*Repeat biopsy from same patient after five weeks on gluten-free diet. Haematoxylin and eosin × 50.*

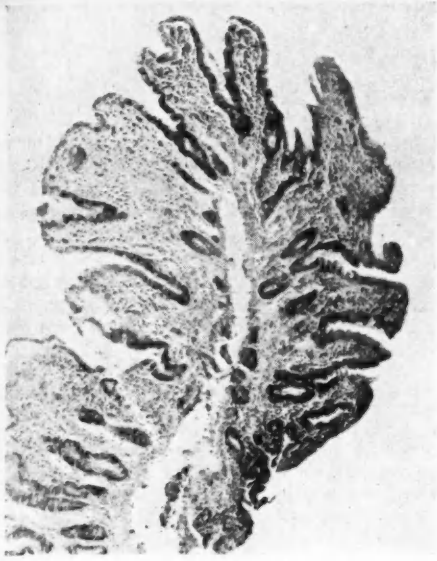

FIG. 6a

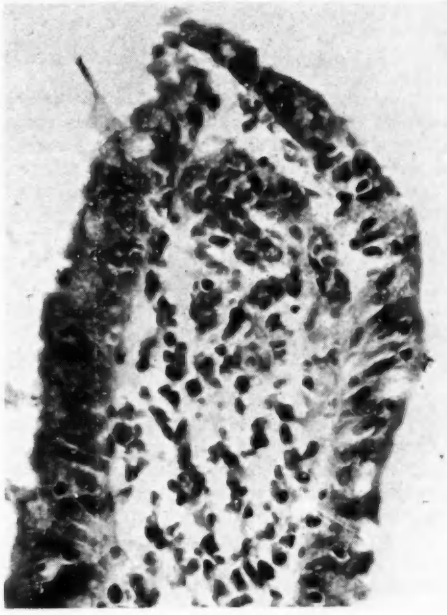

FIG. 6b

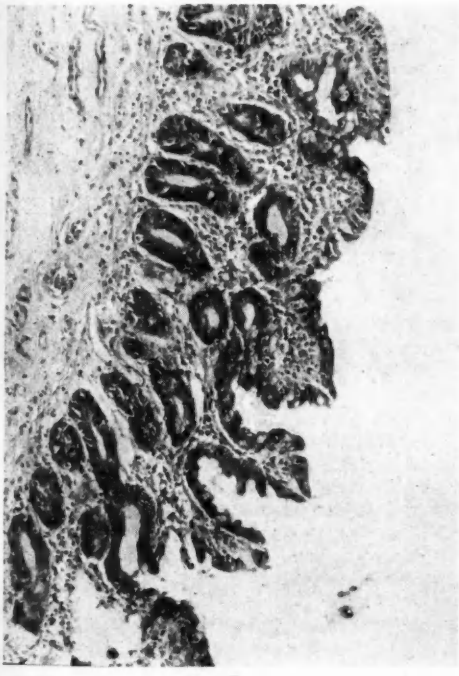

FIG. 7a

FIG. 7b

FIG. 6a.—*Repeat biopsy from same patient after 17 months on gluten-free diet. Haematoxylin and eosin × 50.*

FIG. 6b.—*High-power view of villus from same biopsy. Haematoxylin and eosin × 370.*

FIG. 7a.—*Repeat biopsy from same patient on gluten-free diet 25 months later. Haematoxylin and eosin × 100.*

FIG. 7b.—*Different area of same specimen as in Fig. 7a. Haematoxylin and eosin × 100.*

abnormalities were mainly confined to the idiopathic steatorrhoea group. These abnormalities consisted of villous atrophy, increase in mucosal thickness, and hypertrophy of the glands of Lieberkühn (Shiner and Doniach, 1959), and were possibly due to a defect in cell metabolism at the level of the gland cells which normally give rise to villous cells. Of the 34 adults with idiopathic steatorrhoea investigated, there were five patients in whom a definite history of coeliac disease in childhood was obtained. Histologically the mucosal abnormalities in the patients with or without a history of coeliac disease were identical.

In this report it has been shown that in all eight coeliac patients investigated mucosal abnormalities were found. These abnormalities were the same as in adult idiopathic steatorrhoea, but were possibly more severe. In the youngest coeliac child in this group, aged 2 years 3 months with symptoms for one year, no villi at all were found and the surface epithelium appeared grossly abnormal.

Considering the effect on the small intestinal mucosa of treatment with a gluten-free diet, no difference was found histologically between Cases 1, 4, and 6 previously treated and those almost untreated. In Case 8, repeat biopsies after a gluten-free diet showed that his rapid clinical and biochemical improvement did not correspond with any appreciable histological improvement. Although the overall impression in this patient was that of minor attempts at villous formation following treatment, this would be difficult to judge because of the slight variations normally observed from specimen to specimen obtained at a single biopsy.

My grateful thanks go to Sir Wilfrid Sheldon, Professor D. V. Hubble, Dr. B. E. Schlesinger, Dr. J. Sakula, and Dr. B. D. R. Wilson for permission to study the patients under their care and also for their constant encouragement in this work. I also wish to thank Dr. M. Bodian and Dr. R. A. B. Drury for the histological reports and Mr. J. E. Mayhew for the histological sections.

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*Gut*, 1960, **1**, 55.

# A STUDY OF THE PANCREATIC RESPONSE TO FOOD AFTER GASTRECTOMY IN MAN*

BY

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The results of intubation tests on 50 patients before and after gastrectomy have been reviewed. Following gastrectomy, the pancreatic response to food is modified in the following manner.

(1) There is an increase in the resting volume of secretion.

(2) After a Billroth I operation, the output in one hour after a meal is some two-thirds of the pre-operative output.

(3) After a Polya gastrectomy, the pancreas continues to secrete at its resting rate after meals.

(4) Dissociation of enzymes occurs in the afferent loop after a Polya operation. Lipase is frequently absent from the intestinal contents, and trypsin occasionally so.

(5) Vagal section appears to be an important factor in the production of the new pattern of response.

Experimental studies on dogs have shown that the pancreatic response to food is reduced after gastrectomy (Annis and Hallenbeck, 1952; Richman, Lester, Hollander, and Dreiling, 1954). The early investigations of the problem in man (Stein and Fried, 1923; Glaessner, 1927; Stern, 1929; Santy, Mallet-Guy, Chambon, and Folliet, 1939) do not afford any clear picture of the effect of the operation. The recent work of Lundh (1958), however, has shown that the concentration of pancreatic enzymes in the intestine is very much reduced after gastrectomy, and that a large part of any meal does not mix with the enzymes. Studies with isotopic fat (Shingleton, Isley, Sanders, Floyd, Baylin, Postlethwait, and Ruffin, 1957; Baylin, Isley, Sanders, Reeves, Ruffin, Hymans, and Shingleton, 1957· Ruffin, Keever, Chears, Shingleton, Baylin, Isley, and Sanders, 1958) have indicated that the absorption defect that follows gastrectomy is similar to that occurring in patients with pancreatic deficiency. This may be due either to reduced pancreatic output after gastrectomy or to the meal and pancreatic enzymes mixing poorly.

Dragstedt (1952), Warren (1954) and MacLean, Perry, Kelly, Mosser, Mannick, and Wangensteen (1954) have stated that any modification of pancreatic response following gastrectomy is not important. Indeed, the view of the majority is that inadequate mixing of food and enzymes is one of the features of the post-gastrectomy state (Warren, 1954; Wells, 1955; Polak and Pontes, 1956; Kiekens and Lundh, 1957).

## Present Investigation

The purpose of this paper is to summarize the results of a study of the pancreatic response to food after gastrectomy carried out in Bristol during the past nine years. Intubation tests with a meal were carried out on 50 patients before and after a Billroth I gastrectomy, each patient having four tests, two before the operation to give controls, and two after the operation. The aim of the investigation was to determine the effect of gastric resection on the pancreatic response to food entering the duodenum on the one hand, and entering the jejunum on the other. The tests were therefore grouped as follows:

Series A.—The pancreatic response to a meal entering the duodenum before operation

Series B.—The response to a meal entering the jejunum before operation

Series C.—The response to a meal entering the duodenum after gastrectomy

Series D.—The response to a meal entering the jejunum after gastrectomy.

In each series, 50 results were obtained for analysis, and it is submitted that those in Series C indicate the pancreatic response occurring after a Billroth I operation, and those in Series D afford an approximate index of the response after a Polya operation.

A four-lumen tube was used throughout the investigation, and it was passed under radiological control so as to occupy a position illustrated in Fig. 1. This

* This paper is an abstract of a dissertation submitted for the M.D. degree in the University of Bristol (1959). It was presented at the meeting of the British Society of Gastroenterology at Belfast on November 6, 1959.

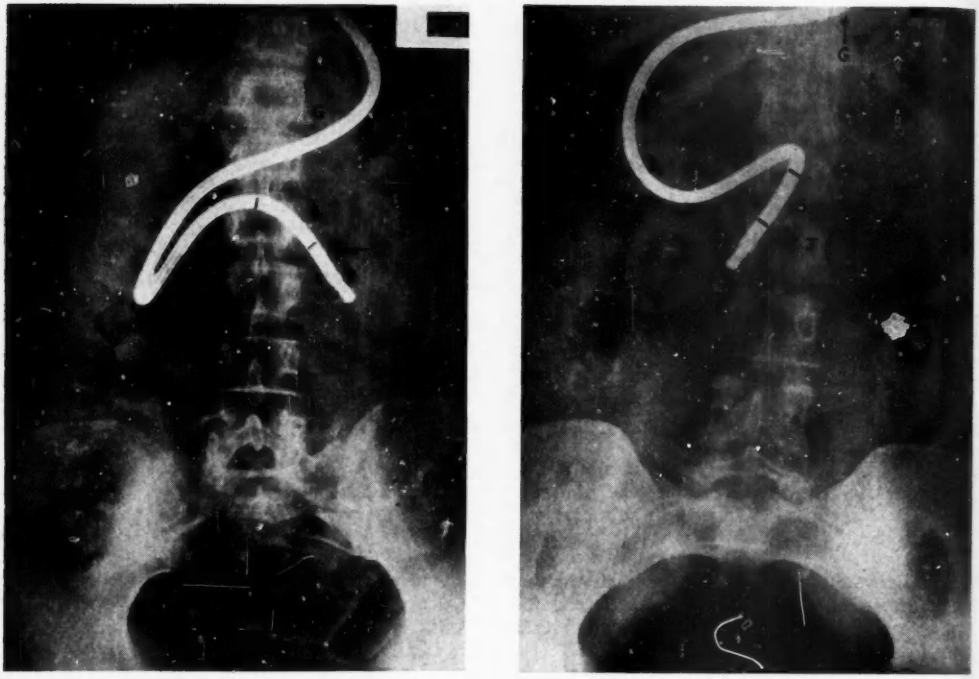

FIG. 1.—*Radiograph of the position of the tube. G = site of holes for gastric suction. J = hole for introducing meal into the jejunum.*

tube afforded access to the jejunum as well as permitting continuous gastric and duodenal aspiration. The general technique of intubation tests is well known, and it will be sufficient to say that the drill followed in these studies was similar to that of Lagerlof (1942) with reference to continuous suction and the treatment of the aspiration samples by ice-cooling and the addition of glycerine. In the tests in Series A and C, when two resting 10-minute samples of duodenal aspirate had been collected, 50 ml. of a meal (Table I) was introduced into the duodenum slowly over a period of four minutes. After two more minutes, the duodenum was emptied, and the aspirate was passed through the appropriate lumen in the tube into the jejunum. The duodenal contents were then collected for one hour in six 10-minute samples.

In Series B and D, resting samples were collected, but the 50 ml. meal was then given through the tube directly into the jejunum. After the lapse of the same time interval as in Series A and C, the duodenal contents were collected for an hour in six samples.

On all the samples, the following estimations were carried out: Volume, bicarbonate concentration and total bicarbonate output per sample, enzyme concentration and total enzyme output per sample. The bicarbonate content was determined by the indirect titration technique of Lagerlof (1942), amylase by the Wohlgemuth method, trypsin by the Lagerlof (1942) method, and lipase by the technique of Cherry and Crandall. To avoid repetition, therefore, the various units referred to in the text are expressed as follows: Amylase in Wohlgemuth units, trypsin in ml. N/10 alcoholic KOH, and lipase in ml. N/20 NaOH.

TABLE I

COMPOSITION OF MEAL FOR INTUBATION TESTS

| | Protein (g.) | Fat (g.) | Carbohydrate (g.) |
|---|---|---|---|
| Whole milk powder (per 100 g.) | 27·5 | 27·0 | 37·5 |
| Reconstituted 1 : 8 | | | |
| 50 ml. contains | 1·72 | 1·7 | 2·34 |
| + hepatovite | 3·5 | — | — |
| + glucose | — | — | 10·0 |
| | 5·2 | 1·7 | 12·34 |

## RESULTS

COMPARISON OF SERIES A AND C.—This shows the effect of gastric resection on the pancreatic response to food entering the duodenum. The general pattern

Enzyme output per 10 minute sample(ml.N/10 KOH) Volume(ml) per 10 minute sample.

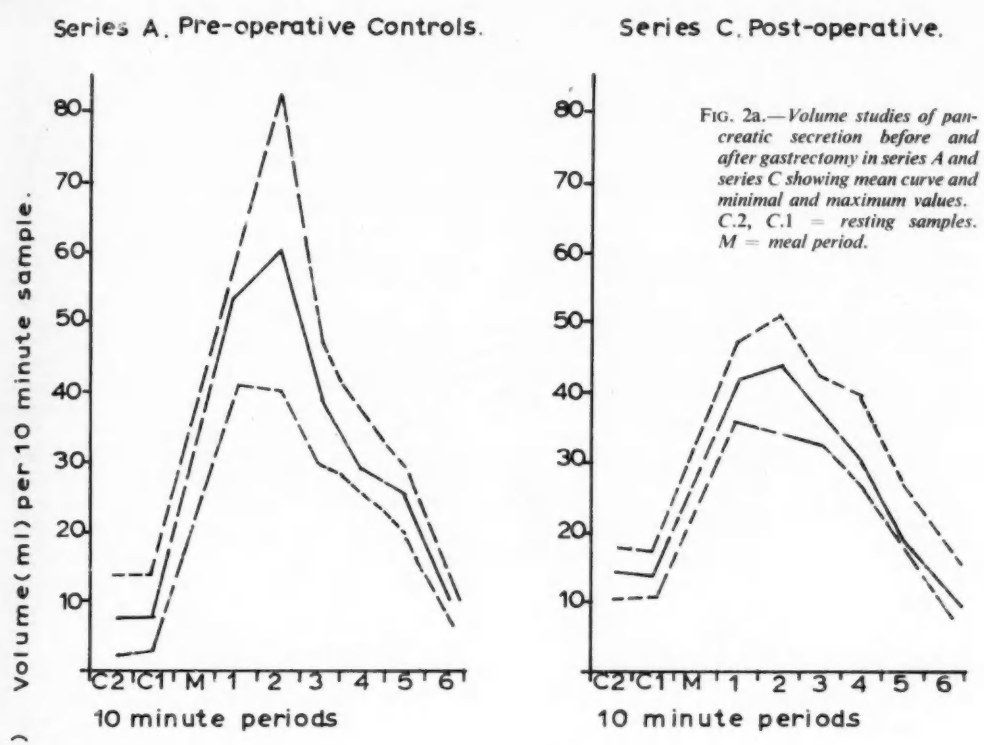


FIG. 2a.—*Volume studies of pancreatic secretion before and after gastrectomy in series A and series C showing mean curve and minimal and maximum values. C.2, C.1 = resting samples. M = meal period.*

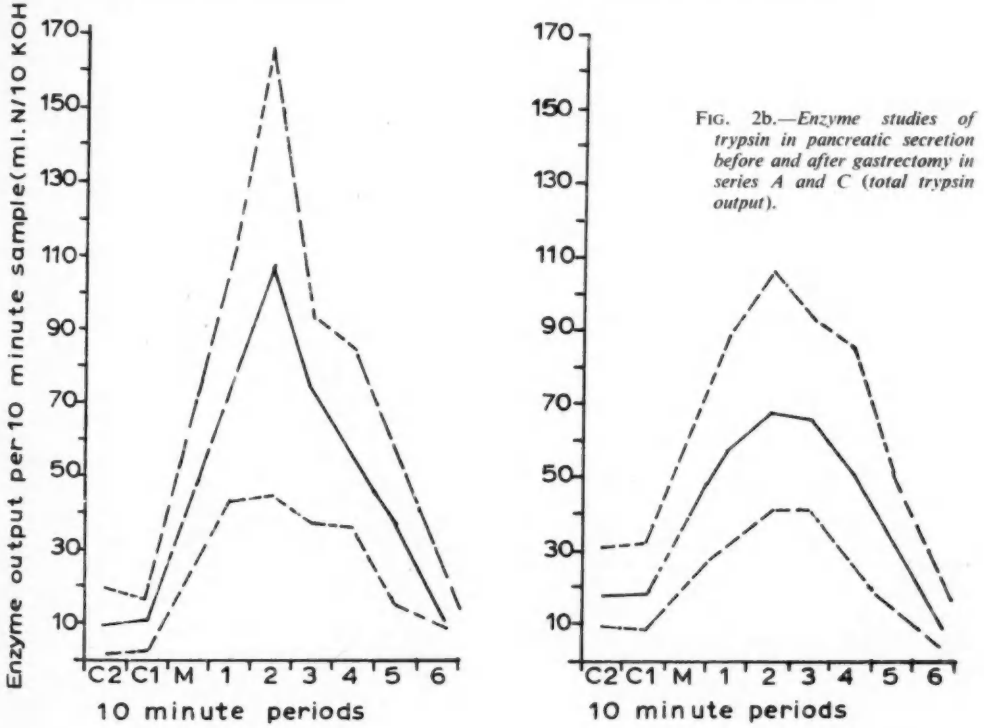


FIG. 2b.—*Enzyme studies of trypsin in pancreatic secretion before and after gastrectomy in series A and C (total trypsin output).*

before and after operation is illustrated in Fig. 2 (a) and (b), but the differences may be summarized thus:

(1) There was an increase in the resting volume per sample in the post-operative series compared with the pre-operative controls. In Series A, the mean 10-minute resting volume was 7·85 ml. (2·4-14·2 ml.), whereas in Series C it was 14·05 ml. (10·5-18·0 ml.). This increase was observed in 45 (90%) of the patients, and in 22 (44%) the post-operative volume was greater than the maximal levels recorded in Series A.

(2) The resting concentrations of bicarbonate and enzymes remained unchanged after operation, and are shown in Table II.

TABLE II

RESTING CONCENTRATIONS OF CONSTITUENTS OF PANCREATIC SECRETION BEFORE AND AFTER GASTRECTOMY

| | Series A | Series C |
|---|---|---|
| Bicarbonate (mEq./litre) | 18·82 (6-34) | 19·15 (12-28) |
| Amylase (units/ml.) | 2,580 (1000-5000) | 2,761 (1000-4444) |
| Trypsin (units/ml.) | 1·2 (0·4-1·7) | 1·28 (0·6-1·9) |
| Lipase (units/ml.) | 114 (91-162) | 107 (81-156) |

(3) After the meal, the variation in the total output in volume and in the various constituents of pancreatic secretion are shown in Table III.

TABLE III

COMPARISON OF PANCREATIC RESPONSE TO DUODENAL MEAL BEFORE AND AFTER GASTRECTOMY (OUTPUT PER 60 min. MEAN ± 1S.D.)

| | Pre-operative Series A | Post-operative Series C |
|---|---|---|
| Volume (ml.) | 219·8 ± 15·7 | 183·9 ± 14·5 |
| Bicarbonate (mEq.) | 12·27 ± 1·47 | 8·20 ± 1·01 |
| Trypsin (units) | 364 ± 38 | 275 ± 61 |
| Lipase (units) | 38,329 ± 3,534 | 27,364 ± 5,778 |
| Amylase (units) | 1,043,950 ± 690,299 | 651,664 ± 231,808 |

In the post-operative series, 46 (92%) of the patients had reduced volume, and in 18 (36%) the new volume was below the minimal values recorded in Series A. The mean reduction in volume for the one-hour period was 36·07 ml. (S.D. ± 20·4 ml.). The bicarbonate concentrations reached in the post-operative series were roughly two-thirds or three-quarters of the values reached in Series A. With reference to the total bicarbonate output for one hour, all the patients showed reduced output after operation, and in 45 (90%) the post-operative level was below the lowest values in the pre-operative controls. The mean reduction was 4.076 mEq. (S.D. ± 1.49 mEq.). The highest enzyme concentrations reached after operation were about half those recorded before operation. The total enzyme output for one hour was also reduced after operation. In the case of amylase, 46 (92%) of the patients had a reduced output, the new level being below the pre-operative range in 20 (40%). In 45 patients (90%), trypsin output was reduced, and in 17 (34%) this was below the minimum pre-operative value. The output of lipase was reduced in 49 (98%) of the patients, being below the pre-operative range in 22 (44%). The mean reductions were as follows:

Amylase ..... 392,292 units (S.D. ± 293,622 units)
Trypsin ..... 89.30 units (S.D. ± 77·0 units)
Lipase ..... 109·64 units (S.D. ± 68·0 units)

(4) The bile content of the samples differed in the two groups. In the pre-operative series, the maximum bile coloration was seen in the first samples in 39 (78%) of the patients, but in Series C, the bile content of the samples was greatest at the end of the hour in 36 (72%) of the patients.

COMPARISON OF SERIES B AND D.—This comparison indicates the effect of gastrectomy on the pancreatic response to food entering the jejunum directly. The general pattern of the response before and after operation is illustrated in Fig. 3 (a) and (b). The observed differences were as follows:

(1) Again, there was an increase in the resting output in the post-operative group, *i.e.*, a mean volume of 12·1 ml. (9-16·2 ml.) per 10-minute sample in Series D compared with 7·7 ml. (2·6-12·0 ml.) per sample in Series B. The increase was recorded in 37 (74%) of the patients, and in 19 (38%) the new value was greater than the maximum levels observed pre-operatively.

(2) The resting concentrations of bicarbonate and enzymes were unchanged and were similar to those shown in Table II.

(3) After the meal, the total output in the two groups is shown in Table IV.

TABLE IV

COMPARISON OF PANCREATIC RESPONSE TO JEJUNAL MEAL BEFORE AND AFTER GASTRECTOMY (OUTPUT PER 60 min. MEAN ± 1S.D.)

| | Pre-operative Series B | Post-operative Series D |
|---|---|---|
| Volume (ml.) | 102·4 ± 6·96 | 78·5 ± 10·6 |
| Bicarbonate (mEq.) | 2·768 ± 0·476 | 2·0344 ± 0·401 |
| Trypsin (units) | 121 ± 15 | 89 ± 19 |
| Lipase (units) | 12,800 ± 1,386 | 8,053 ± 1,204 |
| Amylase (units) | 330,782 ± 72,550 | 187,652 ± 40,652 |

With reference to the volume for the one-hour period, 48 (96%) showed a reduction in Series D compared with Series B, and in 39 (78%) the post-operative volume was less than the minimum observed in the pre-operative series. Indeed, the main feature of the volume response curve post-operatively is that it is virtually flat. Similarly, the

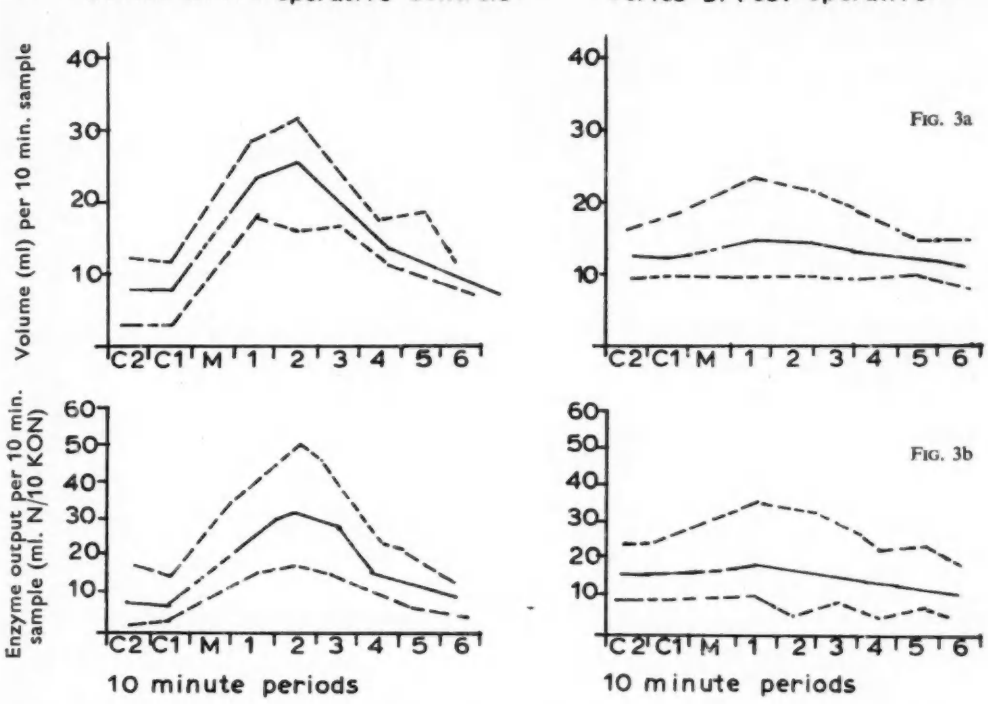


FIG. 3a.—*Volume studies of pancreatic secretion before and after gastrectomy in series B and D.*

FIG. 3b.—*Total trypsin output in pancreatic secretion before and after gastrectomy in series B and D.*

bicarbonate and enzyme concentrations observed in the post-operative series after the meal was given showed minimal variation. The total bicarbonate output for one hour was reduced in 46 (92%) of the patients following operation, being below the lowest values in Series B in 24 (48%). The total amylase output was decreased in 48 (96%) of the patients after operation, and was below the range observed in Series B in 41 (82%). A reduced output of trypsin was recorded post-operatively in 45 (90%) of the patients, and in 39 (78%) the value was below the pre-operative range. The lipase output was found to be reduced in all the patients in the tests in Series D, 48 (96%) having an output below the minimum pre-operative level. The mean reduction for each of the various components mentioned was as follows:

| | | |
|---|---|---|
| Volume | 23·78 ml. | (S.D. ± 13·55 ml.) |
| Bicarbonate | 0·734 mEq. | (S.D. ± 0·650 mEq.) |
| Amylase | 143,125 units | (S.D. ± 90,168 units) |
| Trypsin | 31·48 units | (S.D. ± 25·8 units) |
| Lipase | 47·46 units | (S.D. ± 18·5 units) |

(4) The maximum bile coloration of the samples was observed in the early samples in Series B, but towards the end of the hour period in Series D.

STATISTICAL ANALYSIS.—Since the same patients were subjected to tests in each series, it is permissible to apply statistical criteria to the mean reductions already given. Student's test was used, and it was found that the differences between Series A and C, and between Series B and D were significant ($P < 0.001$).

## DISCUSSION AND CONCLUSIONS

It is evident that one effect of gastrectomy on pancreatic function is to increase the resting rate of secretion. This may account for the so-called compensatory hypersecretion observed by Stein and Fried (1923). A second effect of the operation is a delay in the appearance of bile in the duodenal contents following meals. In this respect, the

findings are in agreement with the observations of Lundh (1958).

With reference to the response to food entering the duodenum, *i.e.*, after a Billroth I operation, the pancreatic output in one hour following the meal is approximately two-thirds to three-quarters of the pre-operative output. Not only is the volume reduced, but the highest concentrations of bicarbonate and enzymes reached are less than those occurring before operation.

When the duodenum is bypassed, and food enters the jejunum directly, the pancreatic response is modified by gastrectomy in a different manner. The characteristic response observed after operation is one in which the pancreas continues to secrete at its new resting rate. By inference, this must resemble the pattern of response to be expected after the Polya operation.

In addition to this primary modification of the pancreatic response after Polya operations, there are other changes of a secondary nature which are related to the creation of the afferent loop. If the contents of this loop are collected as they escape after meals (Butler, 1959), a degree of dissociation of the pancreatic enzymes may be observed. Table V shows that the enzymes are occasionally

TABLE V

FREQUENCY OF ABSENCE OF ENZYMES IN AFFERENT LOOP CONTENTS

| Ante-colic Polya | Controls (30) | Steatorrhoea Group (30) |
|---|---|---|
| Lipase (90 estimations) | 7 (7·7%) | 33 (36·6%) |
| Trypsin (90 estimations) | 3 (3·3%) | 16 (17·7%) |
| Amylase (90 estimations) | 0 | 0 |
| **Retro-colic Polya** | **Controls (16)** | **Steatorrhoea Group (16)** |
| Lipase (48 estimations) | 0 | 14 (29·2%) |
| Trypsin (48 estimations) | 0 | 0 |
| Amylase (48 estimations) | 0 | 0 |

absent or inactivated, lipase more frequently than trypsin, and in patients with long afferent loops more often than those with shorter loops. This change is related to the degree of stasis occurring in the afferent loop, due to its length, its possible denervation, or even to actual obstruction at the stoma. It is probable that this finding reflects the normal instability of the enzymes, for it is known that lipase is notoriously unstable, especially in the presence of trypsin. The latter displays instability also, not so markedly as lipase, but amylase appears to be very stable. Lundh (1958) observed that trypsin was sometimes absent from intestinal contents after gastrectomy but he did not estimate the other enzymes.

To return to the pancreatic responses observed

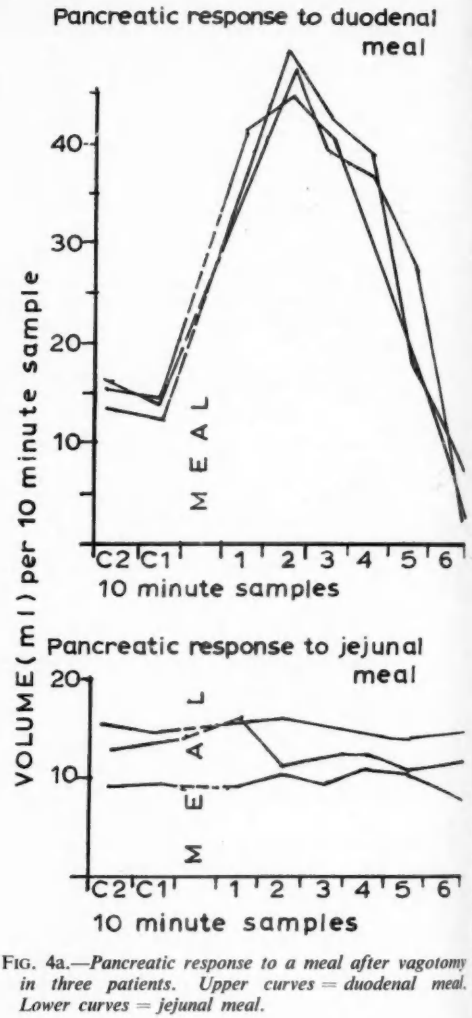


FIG. 4a.—*Pancreatic response to a meal after vagotomy in three patients. Upper curves = duodenal meal. Lower curves = jejunal meal.*

in the tests, especially in Series C and D, the chief problem concerns a possible explanation of the findings. According to the present concept of the control of pancreatic secretion, there is an unimportant psychic phase, no gastric phase, an all-important intestinal phase, involving the secretin-pancreozymin combination, and an uncertain degree of control by the vagus. It is unlikely that altered hormonal release is responsible for the changes observed in the post-operative experiments, since the same meal was given under the same conditions

before and after operation. In the early stages of the study, there were a few opportunities of investigating patients who had had a previous vagotomy. Figs 4 (a) and (b) show the pancreatic response in such patients when a meal was introduced into the duodenum, and into the jejunum directly. The similarity of the responses to those recorded in Series C and D suggests that vagal section, coincident with gastrectomy, may be responsible for the modification of the pancreatic response.

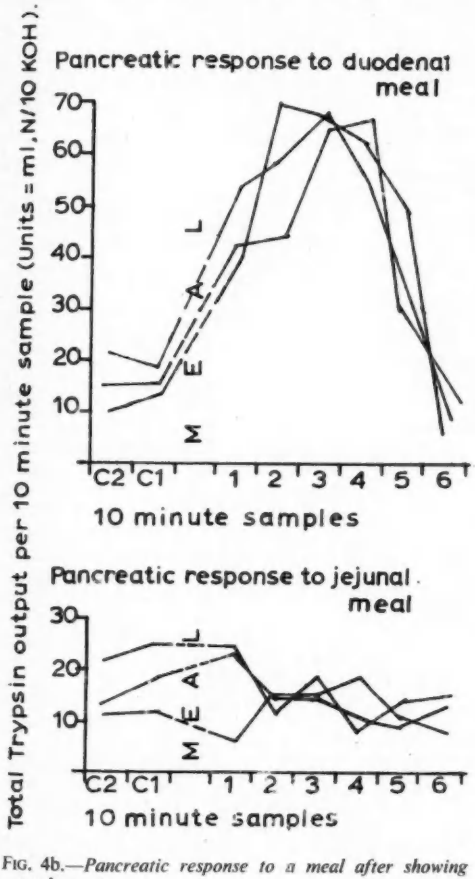


FIG. 4b.—*Pancreatic response to a meal after showing total trypsin.*

It must be stressed that there are several other factors that may be important after gastrectomy. The normal stomach discharges its contents into the duodenum in small amounts, and this almost certainly results in a sustained output from the pancreas, which continues until the stomach is empty. Following gastrectomy, rapid emptying of the stomach remnant may lead to the production of pancreatic secretion over a shorter period of time. The duodenum following a Polya operation is bathed in alkaline secretion, and this factor may cause further reduction in pancreatic output. Finally, since some of the post-cibal syndromes occuring after operation are mediated by sympathetic nervous pathways, pancreatic secretion may be inhibited if the reflexes involve the pancreas.

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*Gut*, 1960, **1**, 62.

# INTESTINAL PSEUDO-OBSTRUCTION WITH STEATORRHOEA*

BY

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A hitherto undescribed syndrome is recorded. Its features are gross overactivity of the small intestine with episodes of obstruction, but without any mechanical factor being found, and steatorrhoea. In one patient the inner circular coat showed gross hypertrophy.

In the past few years we have encountered three cases of intractable wasting and diarrhoea in which attacks of intestinal pseudo-obstruction have occurred. Two of them will not be discussed in detail because in one, a woman of 52 years, the jejunum showed the histological appearances of adult coeliac disease as described by Paulley (1954) and Shiner (1956). At laparotomy the peristaltic activity of the small intestine was grossly abnormal, showing violent segmentation movements. It was impossible to alleviate her condition, from which she had suffered for 20 years, and she has recently died elsewhere, some three years after coming under our care. Another patient, a woman, aged 56, who in four years had two attacks of pseudo-obstruction leading to laparotomy and lost 70 lb. from steatorrhoea, was eventually explored for a perforation, and a very small reticulo-sarcoma of the ileum was found, from which she died soon after. It is extremely doubtful whether this sarcoma could have accounted for the long preceding history.

Our third patient, a man aged 36, has been carefully investigated both by us and by Dr. Avery Jones at the Central Middlesex Hospital, and so far we have not been able either to find a known cause for his condition or to alleviate it substantially. The main features of this case, similar in many respects to the two previously mentioned, are (1) a long history of colicky, abdominal pain; (2) fatty diarrhoea, malabsorption, and loss of weight; (3) gross abdominal distention with audible and visible intestinal peristalsis; (4) episodes of pseudo-obstruction; (5) no mechanical cause for obstruction found at laparotomy; (6) marked segmentation movements of the gut visible radiologically and at laparotomy; (7) absence of hydroxyindoleacetic acid in the urine and absence of gastric hypersecretion (800 ml. per 24 hr.), no anaemia, normal erythrocytic sedimentation rate, and no L.E. cells.

## Case Report

Case 1.—B, a man aged 36, began to have abdominal symptoms of pain and discomfort in 1947 when aged 24. A duodenal ulcer was diagnosed radiologically and he obtained some relief of symptoms by dietary treatment. In 1953, when aged 30, he had an emergency appendicectomy but abdominal colic and post-prandial discomfort continued after this. Mild diarrhoea occurred from time to time, and by 1957, the pattern of symptoms was established as noisy abdominal colics at all times of day but worse after meals; three or four loose stools a day; some abdominal distention and progressive loss of weight. A barium meal at this time showed only rapid gastric emptying.

In May, 1958, when in Weston-super-Mare Hospital for the investigation of his symptoms, he developed more severe abdominal pain and tenderness, a rapid pulse, and signs of shock. He was treated conservatively and discharged from hospital, but was readmitted six weeks later with abdominal pain and vomiting. A laparotomy showed that a small abscess cavity had formed in the lower peritoneum from a minute perforation of the small intestine. The terminal ileum appeared to be in spasm but there was no evidence of regional ileitis.

A barium meal in September, 1958, showed great dilution of the barium in the small gut. A blood count and the E.S.R. were normal.

On November 20, 1958, he was admitted to Southmead Hospital, Bristol, where the findings were: Weight 103 lb., a distended abdomen, which showed phases of visible and audible peristalsis accompanied sometimes by pain. The stools were greasy in appearance with a mean daily fat excretion over three days of 17 g. Sigmoidoscopy showed an oedematous mucosa which, on biopsy, appeared normal. A straight radiograph of the abdomen showed distended coils of small bowel (Fig. 1).

Barium studies were fraught with difficulties due to delay in stomach emptying and to great dilution of the

*Presented at the meeting of the British Society of Gastroenterology in Belfast, November 6, 1959.

barium in the small bowel. Segmentation movements were observed and the barium, which flocculated easily, was shuttled back and forth in the loops of intestine.

In December, 1958, he had a seven-day phase of increased abdominal colics and hyperperistalsis.

On December 16, 1958, laparotomy (W.M.C.) was performed and a reddened small intestine covered with flakes of fibrinous exudate was found. Peristalsis was very active and segmentation movements marked. The wall of the small intestine was possibly oedematous.

A biopsy of liver and peritoneal fibrin nodules showed no specific pathology. Biopsy of the jejunal wall showed normal mucosa, submucosa, and muscularis mucosae, but a greatly thickened inner muscular coat with a good deal of vacuolation of the muscle fibres.

After operation, the patient was given a gluten-free diet and this has been continued to date without clear-cut improvement.

From January 20, 1950, he was given "prednisone", 40 mg. per day, with potassium chloride by mouth, but this seemed to make no difference and he was weaned off it after two months.

He had a further attack of pseudo-obstruction on January 31, 1959, but this was successfully treated by intravenous therapy and intestinal suction.

Twenty-four-hour gastric aspiration showed no evidence of hyperchlorhydric hypersecretion (800 ml.

FIG. 1.—*Barium in the small intestine.*

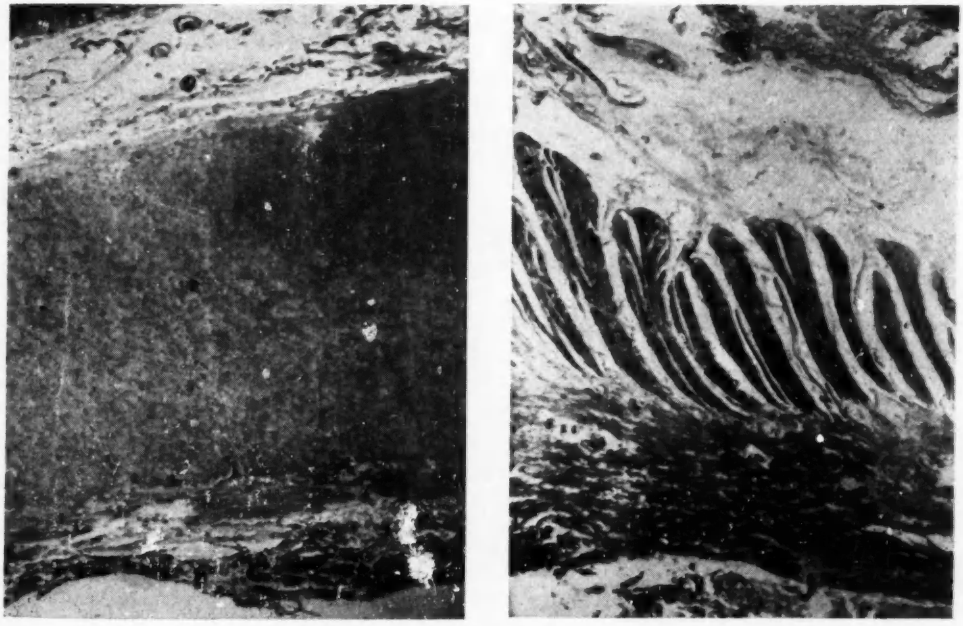

FIG. 2.—*Section of patient's small intestine (left) with serosa at the bottom, showing thickened inner or circular muscle coat, with a section of normal small intestine for comparison (right).*

per 24 hours). The urine contained no excess of hydroxyindoleacetic acid but large quantities of indican.

The patient was subsequently reinvestigated by Dr. Avery Jones at the Central Middlesex Hospital with similar findings and on intraluminal biopsy of the jejunum Dr. Shiner confirmed the normal mucosal appearances. Radiologically it was then impossible to fill the terminal ileum, and possible diagnoses of intraluminal tumour or an achalasia of the ileocaecal valve were considered. However, a further abdominal exploration was not considered justifiable.

Subsequently the patient has been able to resume work. He continues to take a gluten-free diet. He has had in the past six months two attacks of pseudo-intestinal obstruction, the first a minor one treated by a day's gastric aspiration and rest, the second a more prolonged affair when continuous gastric suction and intravenous therapy had to be continued for several days, following a severe mental shock.

The state of the abdomen varies greatly from day to day and hour to hour. Phases of great distension are followed by phases of loud peristaltic activity and occasionally the abdomen is relatively flat. The patient is anxious to keep working and to avoid further operations.

*The Morbid Anatomy of the Gut.*—The appearances of the small intestine at laparotomy were notable dynamically, segmentation movements being most pronounced. In addition the gut was hyperaemic and the intestinal wall appeared thickened. On histological examination the most striking feature was the thickness of the inner circular muscle coat, which is about 10 times the thickness of the outer or longitudinal coat (Fig. 2). Through the kindness of Dr. Paulley we were able to examine several of his sections of normal small intestine obtained at operation, and these, though they show the difficulty of measuring the thickness of muscle coats due to varying directions of the cut, are quite different because in none is the inner coat more than four times the thickness of the outer coat.

The hypertrophied inner muscle shows marked vacuolation of the fibres and this feature is also present, though less noticeably, in the outer coat. The muscle fibres of the inner coat have indistinct outlines but in both coats the nuclei appear normal. The ganglion cells and nerve fibres of Auerbach's and Meissner's plexuses show no abnormality.

## Discussion

This case presents us with many problems. First, have others encountered a similar clinical problem? There is no reference in the literature to a condition specifically like this one, but there are a number of cases described which are similar in many respects. In the literature concerning steatorrhoea, there are cases recorded where obstructive symptoms have developed leading to useless laparotomy. Cooke, Peeney, and Hawkins (1953) quote two patients with adult steatorrhoea who had recurrent intestinal colic, but both were relieved to a certain extent of their symptoms by potassium repletion. One of them had a negative laparotomy.

Ingelfinger (1943) also describes a patient with steatorrhoea of 15 years' duration who suddenly had episodes of intestinal obstruction. At laparotomy the gut wall was reported as loose and flabby. Two ileostomies were carried out at different times, and later closed after the malabsorption state had been thoroughly treated. Even so the patient still suffered from cramps and noisy gut activity.

Murley (1959) has described the case of a woman with multiple sclerosis and migraine who had symptoms of intermittent intestinal obstruction. There was steatorrhoea, radiological evidence of disordered peristalsis in the duodenum and jejunum with backwash into the stomach, and at operation the jejunum was thickened and the duodenum dilated. Biopsy showed no specific features of any known disease. Dr. Murley has kindly let us see sections of the small intestine from this patient, which do not show the thickening of the inner muscle coat observed in our patient. Oedema of the muscular coat and a degree of cellular infiltration in Dr. Murley's specimen may fall within the limits of the normal.

Ihre (personal communication, 1959) has told us of a patient of his, a 35-year-old man who began to suffer from abdominal pain and meteorism in 1951. Five years later he was worse and had lost 5 kg. in six months. Abdominal distension occurred in bouts every afternoon and was somewhat relieved by passing wind. Two years later, vomiting, diarrhoea, and steatorrhoea were all noted again, as well as the radiological appearance of dilated intestines. A laparotomy revealed no mechanical cause for the obstructive symptoms nor any specific pathology. Only intravenous feeding prevented the attacks of pseudo-obstruction. Jejunostomies were performed in the next two months, but without improvement and he died, necropsy revealing no explanation for the cause of the malady.

Pilkington (personal communication, 1959) has described to us the case of a man with diabetes and polyneuritis who developed marked abdominal distention and steatorrhoea. Laparotomy was carried out but the clinical suspicion of Whipple's disease was not borne out by the histological findings. Abdominal distension and vomiting continued until death ensued six months later. Necropsy revealed no cause for the condition, though the small intestine was found to be distended and thickened in places. We have been privileged to examine this specimen which shows none of the apparent muscular hypertrophy observed in our

TABLE I

MAIN FEATURES OF SOME CASES OF PSEUDO OBSTRUCTION WITH STEATORRHOEA

| Patient and Age | Length of History (in years) | Vomiting and Distention During Attacks (Pseudo Obstruction) | Steatorrhoea and Weight Loss | Noisy and Disordered Peristalsis | Gut Histology |
|---|---|---|---|---|---|
| Male 36 (Naish and Capper) | 10 | ++ | ++ | ++ | Inner muscular coat hypertrophied, mucosa normal |
| Male 36 (Ihre) | 7 | ++ | ++ | ++ | Not obtained |
| Male 26 (Pilkington) | 1 | Continuous distention and vomiting | +++ | + | Muscle coats normal, mucosa autolysed |
| Female 50 (Murley) | 2 | Vomiting only, no distention | ++ | ++ | Muscle coats normal, mucosa normal |
| Female 46 (Dudley *et al.*) | 16 | ++ | | + | No laparotomy |
| Female 73 (Lang Stevenson) | | ++ | ++ | ++ | Muscle coats hypertrophied, diverticula present |
| Female 50 (Naish and Capper) | 16 | + | +++ | ++ | Resembles adult coeliac disease |

case. The mucosa has been damaged by post-mortem digestion and no opinion can be reached on its living state.

Dudley, Sinclair, McLaren, McNair, and Newsam (1958), in reviewing the clinical problem of intestinal pseudo-obstruction or "spastic ileus", record a number of cases where laparotomies were undertaken to relieve a mechanical obstruction which was not found. Their Case 4, a woman aged 46, had bouts of abdominal pain and vomiting for 16 years. Radiographs showed distended loops of intestine and multiple fluid levels and a mouthful of barium remained in the pyloric region for days. In the light of previous experience, conservative treatment was advised.

Lang Stevenson (personal communication, 1959) has drawn our attention to a patient, a woman aged 73, who suffered from repeated vomiting and steatorrhoea and whose jejunum showed disordered and ineffective peristalsis which was visible through the abdominal wall, radiologically and at laparotomy. This patient also had a number of duodenal and jejunal diverticula for which she underwent operation. She gave a six months' history of noisy intestinal rumbling and a shorter history of pain and projectile vomiting of food eaten up to 12 hours previously. She had lost 14 lb. in weight and her haemoglobin was 8·4 g.%. Peristalsis was easily visible through the abdominal wall, and appeared to pass to both right and left. Laparotomy showed dilatation and hypertrophy of the duodenum and the jejunum with diverticula in both areas. In the jejunum, waves of peristalsis were very active and passed in both directions, the gut writhing violently. Beyond the affected area, peristalsis was orderly and tailwards.

Three duodenal diverticula were removed and the affected area of jejunum (2 ft.) excised, continuity being restored by end-to-end anastomosis. A retrocolic gastro-jejunostomy was also done. After operation the patient did well, lost her symptoms, and regained her former weight.

Microscopical sections of small intestine kindly forwarded to us show striking changes in the muscular coats. The appearances vary a little in sections from different levels but in most the inner muscle coat is considerably thicker than the outer. Where this feature is most marked the nuclei of the muscle fibres of the outer coat are very abnormal, many being greatly increased in size and of bizarre pattern and shape. Vacuolation of muscle fibres is not seen in the inner coat but is present to a slight degree in the outer coat. The mucosa, submucosa, muscularis mucosae, and nerve plexuses appear normal. In the diverticula both muscle coats are thinned out but no other special features are seen.

The features of the cases described are none of them uniform but in all there was evidence of disintered peristalsis of the small intestine, attacks of vomiting and distention, diarrhoea with steatorrhoea, and loss of weight (Table I).

The second major problem posed is the reason for the increased but ineffective peristaltic activity of the small intestine in our case and these other similar cases. Could this be due to an immobile segment of gut at the ileo-caecal valve, comparable with the condition of achalasia of the oesophagus or congenital megacolon? Against this hypothesis

is the absence of any evidence for such a state of affairs in our case at laparotomy, and the absence of any loss of ganglion cells. In other cases the condition appeared to affect the jejunum only. Furthermore increased peristaltic activity is a feature neither of oesophageal achalasia nor of megacolon.

Could the increased peristalsis and segmentation be due to the presence of excess quantities of a chemical substance such as serotonin? None of the end-products of serotonin breakdown have been found in the urine, and the presence of large quantities of urinary indican may be a reflection only of the stagnation of intestinal contents.

Speculation as to possible causes leads us to look for possible clues from the study of other similar but not identical cases. Two of the patients, Murley's and Pilkington's, had diseases of the central nervous system which could conceivably have affected the central connexions of the autonomic nerve fibres supplying the gut. The comment of the surgeons, who were shown the film of our patient's intestinal behaviour at laparotomy at a meeting of the Surgical Section of the Royal Society of Medicine, was that the patient must have been under spinal anaesthesia. This was not so. But could he have some disease of the spinal cord or its autonomic outgoing connexion which produces the same effects on movement of the gut as spinal anaesthesia? Is perhaps the inhibiting control exercised by the spinal cord and the autonomic nervous system more important in the smooth regulation of gut peristalsis than we are accustomed to recognize? We tend perhaps to regard tailward peristalsis as an innate function of a tube of smooth muscle and we regard the autonomic nervous system merely as the controller of valves and the speed of transit. Anyone who has witnessed the acute abdominal distension and ileus of a patient with an extradural vertebral abscess may doubt this; and the case of the patient we have described must stimulate thought on the mechanisms controlling a process which in most humans is so trouble free.

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# DIAGNOSTIC SIGNIFICANCE OF D.XYLOSE EXCRETION TEST

BY

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This paper assesses the use of d.xylose as a test of function of the small intestine. In general d.xylose excretion is associated with disturbance of the intestinal wall of the upper jejunum. Low readings are found with adult coeliac disease but rarely with regional enteritis.

The excretion of d.xylose in the urine after the ingestion of a known quantity is used as a test of intestinal absorption. In particular, its use in conditions associated with steatorrhoea has been reported by Fourman (1948), Brien, Turner, Watson, and Geddes (1952), Gardner and Perez Santiago (1956), Benson, Culver, Ragland, Jones, Drummey, and Bougas (1957), Finlay and Wightman (1958), and Butterworth, Perez Santiago, Martinez-de Jesus, and Santini (1959). The purpose of this paper is to assess this test as a routine diagnostic measure in the investigation of disorders of the small intestine.

## Material and Methods

d.Xylose, 25g. in 250 ml. of water, was administered to patients and normal subjects in the fasting state. A further 250 ml. of water was taken at once and again one and two hours later, *i.e.*, approximately 1 litre of water in all. The bladder was emptied voluntarily at the beginning of the test and all urine passed in the five hours after the ingestion of d.xylose was collected and kept in a refrigerator until analysed. Storage in the cold for periods of at least a week made no difference to the results. Though the majority of patients were confined to bed during the performance of the test, the normal subjects and out-patients were ambulant.

d.Xylose was determined by the method of Roe and Rice (1948). In a number of patients, the folic acid excretion test (Cox, Meynell, Cooke, and Gaddie, 1958), jejunal biopsy (Crosby and Kugler, 1957), haematological survey, intestinal radiology, and determination of faecal fat were performed.

Control data were provided by 43 normal subjects, 31 medical students and hospital staff (18 men and 13 women aged 20-50), and 12 hospital patients without anaemia or intestinal disorder (four aged 33-62 and eight aged 69-98 years). One hundred and thirty-six patients were also studied, suffering from various disorders as indicated in Table I and detailed further in the results of the investigation.

## Results

The results in the various groups of subjects are summarized in Table I.

Forty-three Normal Controls.—Inspection of the results showed that the eight subjects aged 65 and over had a mean d.xylose excretion of 2·85 g. (S.E. 0·10) whereas 35 subjects under the age of 65 years had a mean excretion of 7·24 g. (S.E. 0·27) in

Table I

FIVE-HOUR URINARY EXCRETION OF D.XYLOSE IN 179 SUBJECTS AFTER ORAL INGESTION OF 25 G. D.XYLOSE

| Diagnosis | Under 65 Years | | | | Over 65 Years | | | |
|---|---|---|---|---|---|---|---|---|
| | No. of Subjects | Range (g.) | Mean (g.) | S.E. | No. of Subjects | Range (g.) | Mean (g.) | S.E. |
| Normal | 35 | 4·8—11·5 | 7·2 | 0·25 | 8 | 1·5—4·1 | 2·9 | 0·30 |
| Regional enteritis | 17 | 3·6—9·5 | 6·0 | 0·41 | 0 | — | — | — |
| Pancreatitis | 12 | 4·2—10·7 | 6·3 | 0·51 | 1 | — | 3·4 | — |
| Ulcerative colitis | 13 | 4·2—9·4 | 6·7 | 0·42 | 0 | — | — | — |
| Entero-colitis | 4 | 4·5—9·5 | 7·0 | — | 0 | — | — | — |
| Cirrhosis | 9 | 4·2—8·0 | 6·2 | 0·48 | 0 | — | — | — |
| Pernicious anaemia | 7 | 2·8—6·5 | 4·9 | — | 3 | 1·7—3·0 | 2·4 | — |
| Megaloblastic anaemia of pregnancy | 7 | 1·6—7·4 | 4·7 | — | 0 | — | — | — |
| Partial gastrectomy | 8 | 4·3—10·3 | 6·1 | 0·69 | 5 | 3·0—5·8 | 4·3 | — |
| Miscellaneous | 25 | 2·7—11·2 | 5·9 | 0·42 | 3 | 2·6—5·8 | 4·7 | — |
| Adult coeliac disease | 20 | 0·4—5·3 | 2·8 | 0·31 | 2 | 2·3—3·1 | 2·7 | — |

five hours. The mean urine volume, 319 ml., was much less than the mean urine volume, 667 ml., of the larger number of younger subjects. Partial correlation between xylose and volume in the younger group of 35 subjects ($R = + 0{\cdot}27$) and the whole group of 43 subjects ($R = + 0{\cdot}26$) was not significant. On the other hand, partial correlation between age and xylose in the younger group was not significant ($R = - 0{\cdot}22$) but was significant in the whole group of 43 subjects ($R = - 0{\cdot}65$) at the 1% level. The lower limit of normal was, therefore, set at 4·2 g. in five hours, *i.e.*, 7·24 − 2 S.D., and lower results in any patient aged 65 and over were not regarded as being indicative of any abnormality.

TWENTY-TWO PATIENTS WITH ADULT COELIAC DISEASE.—Inspection of the data indicated that neither age nor low urine volumes were responsible for the poor excretion of d.xylose in this group. Two patients excreted 5·3 and 4·9 g. respectively. One of these had been controlled clinically by a gluten-free diet for five years though he still had some excess of fat in his faeces. The second patient, a girl aged 19, had had severe coeliac disease and though not on a gluten-free diet was clinically well. Both had abnormal folic acid excretion tests and characteristically abnormal jejunal biopsies. Though other patients were clinically well either on a gluten-free diet or steroid therapy, none showed normal xylose excretion or normal folic acid excretion.

THIRTEEN PATIENTS WITH PANCREATITIS.—There was one abnormal result, 3·4 g., in a 68-year-old woman. In the remaining patients, d.xylose excretion was normal, ranging from 4·2 to 10·7 g. The 35-year-old patient with the borderline result of 4·2 g. had steatorrhoea responding to therapy with pancreatin, repeated upper respiratory and lung infections, bronchiectasis, and abnormalities in the $\gamma$-globulin fraction of the serum proteins, agglutinins to B group being almost absent and a fast moving component of the $\gamma$ fraction deficient on immune electrophoresis.

TEN PATIENTS WITH PERNICIOUS ANAEMIA.—Abnormal results were encountered in five. Of these, four were aged 61, 76, 76, and 79 years, and a 35-year-old woman before therapy, who fulfilled acceptable criteria for the diagnosis of pernicious anaemia, namely, histamine-fast achlorhydria, megaloblastic bone marrow, normal faecal fat excretion, low serum B.12, normal haematological response to B.12, and a normal jejunal biopsy. She did, however, show an unusual amino-aciduria for which we have no adequate explanation at present. All patients had a normal faecal fat excretion. Of the five patients who had normal results, four had received B.12 therapy and one had had a folic acid excretion test. The three oldest patients with abnormal results had also received B.12 therapy but neither the man aged 61 nor the woman aged 35 had done so.

THIRTEEN PATIENTS WITH POST-GASTRECTOMY STATES.—The only abnormal results were encountered in three patients who were over 65 years of age.

THIRTEEN PATIENTS WITH ULCERATIVE COLITIS AND FOUR WITH ENTEROCOLITIS.—These gave normal results. All the patients were aged less than 65.

NINE PATIENTS WITH CIRRHOSIS OF LIVER.—No abnormal results were encountered though one patient was more than 65 years old.

SEVENTEEN PATIENTS WITH REGIONAL ENTERITIS.—Only two low results were encountered. One, 3·7 g., was in a 35-year-old man with extensive intestinal involvement and a high jejuno-ileal fistula. The urine volume was, however, low (97 ml.) so that a small error in collection might have accounted for this abnormal result. The other, 3·6 g., was in a 23-year-old woman with jejunal involvement radiologically demonstrated.

SEVEN PATIENTS WITH MEGALOBLASTIC ANAEMIA OF PREGNANCY.—Two abnormal results were obtained. One patient aged 20 had previously been diagnosed as "idiopathic steatorrhoea" and was taking folic acid when first seen. Faecal fat determinations, however, during pregnancy and again in the puerperium were normal. A folic acid excretion test was abnormal. In the second, no steatorrhoea was present and there was no history of previous illness. On the other hand, one normal result (4.8 g.) was encountered in a 23-year-old woman in her second pregnancy in whom steatorrhoea was present.

TWENTY-EIGHT PATIENTS WITH MISCELLANEOUS DISORDERS.—Five patients were investigated for diarrhoea for which no organic cause could be identified. In each, faecal fat excretion, intestinal radiology, a full haematological survey, urine chromatography, folic acid excretion, glucose tolerance, and xylose excretion tests were all normal. Two patients with macrocytic anaemia, steatorrhoea, and extensive short circuits of the small intestine excreted 5·8 and 8·4 g. respectively even though the first patient was 67 years of age. One patient, with an argentaffinoma tumour of the small intestine and extensive deposits in the mesentery, excreted 5·8 g. One patient with an ileostomy excreted 5·8 g.

and one patient with pancreatitis, agammaglobulinaemia, and steatorrhoea 5·3 g. Two patients with extensive diverticula of the small intestine involving the jejunum, macrocytic anaemia, and steatorrhoea excreted 3·3 and 2·9 g. respectively. One patient aged 54, with a chronic atrophic fibrosing process of the jejunum, excreted 3·2 g. Another woman aged 54, with a history of 20 years of persistent hypochromic anaemia possibly due to hiatus hernia and oesophagitis, normal jejunal biopsy, and steatorrhoea, only excreted 3·8 g.

## Discussion

d.Xylose is absorbed in the upper small intestine (McCance and Madders, 1930) and in rats over 90% of the ingested dose has disappeared from the intestines in one hour (Butterworth *et al.*, 1959). The bulk of evidence suggests that phosphorylation is involved in the absorptive mechanism of xylose (Hele, 1953; Ota and Shibata, 1954). Approximately 40 to 45% of an ingested dose of d.xylose in man is excreted in the urine in 24 hours (McCance and Madders, 1930; Wyngaarden, Segal, and Foley, 1957; Butterworth *et al.*, 1959). d.Xylose that is metabolized is incorporated into liver glycogen (Hiatt, 1957) whilst Wyngaarden *et al.* found that 13·5% of a dose of d.xylose I.C.[14] given intravenously in man is excreted as carbon dioxide.

As Finlay and Wightman (1958) hinted, d.xylose excretion did appear to diminish in the older age groups and we found it necessary to discount abnormally low results in patients 65 years and older. As was shown by McCance and Madders (1930), d.xylose excretion was independent of urine volume in both the young and old subjects in our control series.

There is some variation in the reported amounts of d.xylose excreted by normal subjects in five hours. The mean excretion varies from 5·6 to 6·7 g. Using the limit set by the mean less twice the standard deviation, the lowest limit of normal is 2·9 g. reported by Butterworth *et al.* in 100 Puerto Rican subjects aged 18 to 26 and 14 hospital laboratory staff aged 20 to 50 years, the largest group that has been studied. Our findings gave a mean excretion much higher than others. The reason is not immediately apparent but our lower limit is set at the same level as that used by Benson *et al.* This variation of the reported normal excretion in five hours does impose some restriction on the random use of the test but less than 3 g. can safely be assumed to be abnormal.

The blood xylose levels were not investigated in our patients for two reasons, first to keep the test as simple as possible, and secondly, to avoid the inherent difficulty of assessing any absorption curve. However, Benson and his colleagues have suggested that blood xylose levels should be estimated two hours after the test dose. The finding of normal levels and low urinary excretion indicates, in their view, impaired renal excretion. In those patients in whom we were unable satisfactorily to explain low urinary excretions, routine kidney function tests, including creatinine clearance, did not appear to account for our findings.

The high incidence of low results in the control subjects and patients over the age of 65 compelled us to place no significance on such low values. Thus, in pernicious anaemia low values were found in four patients aged 61 to 79. Helmer and Fouts (1937) were unable to demonstrate any consistent abnormality in excretion of d.xylose in 48 patients with pernicious anaemia. Of these, 30 excreted less than 4·2 g.; of these 30 patients, 19 had a urea clearance of less than 70% and of these 10 were over 60 and the age of one was not known. Of the remaining 11 patients, five were over 60. There remained six who had a low d.xylose excretion for which no reason was apparent. It is possible that some may have had intestinal disorders had modern diagnostic procedures been used. We have concluded that the finding of a five-hour d.xylose excretion of less than 4·2 g. in a patient under 60 makes the diagnosis of pernicious anaemia uncertain.

Benson *et al.* (1957) found that seven out of 13 of their patients who had undergone partial gastrectomy had low results; two of these were aged 65 and 67, though three patients aged 61 all had normal results. In our patients, the only two abnormal results were in elderly patients aged 65 and 71. We consider that the test can offer little additional information in this group of patients. In regional enteritis, the only two patients to have some involvement of the jejunum had a low excretion, though in one this finding could have been attributed also to the low urine volume. These results contrast with those reported by Benson *et al.* who reported that two out of four patients with regional ileitis had a low excretion.

Both Benson *et al.* (1957) and Finlay and Wightman (1958) found that some patients with adult coeliac disease had normal d.xylose excretion. In our two patients there seems little doubt as to the correctness of the diagnosis, according to present-day criteria. It has also been reported that improvement in xylose excretion takes place with clinical remission (Finlay and Wightman, 1958) though in our patients this was not significant in the few patients in whom the tests have been repeated or in those who had been under treatment for a long time.

The presence of severe liver dysfunction made no difference to the test for the results in our patients with cirrhosis were normally distributed around our mean normal excretion. Butterworth *et al.* (1959) showed that d.xylose was excreted in significantly greater quantities if the liver was by-passed and Wyngaarden *et al.* noted that d.xylose was removed more slowly from the blood in patients with cirrhosis. Hence though the five-hour excretions are within the normal range the results do not necessarily imply that the absorption mechanism is normal.

It is evident both from our results and those recorded in the literature that d.xylose excretion is normal in pancreatitis with steatorrhoea. Gardner and Perez Santiago (1956) have reported on the usefulness of this test in tropical sprue. They found d.xylose excretion consistently low in the untreated patients and no significant difference in the results of a group of patients already on treatment, many for months or years. Butterworth *et al.* (1959) in a more extended study did show an improvement in the mean excretion in treated patients with sprue, the mean excretion of 49 untreated patients being 1·4 g. (S.D. 0·7) and of 28 treated sprue patients 3·5 g. (S.D. 1·3). Only one patient with tropical sprue has been investigated by us. In her the excretion was low, 1·5 g.

As a result of our experiences in the use of this test we believe that it provides useful information in patients with a macrocytic anaemia other than those in whom previous surgery on the stomach or small intestine has been carried out. Certainly the finding of low xylose excretion in a patient with "pernicious anaemia" should necessitate the fullest investigation before such a diagnosis can be considered substantiated. Similarly the finding of a normal d.xylose excretion test in a patient with "adult coeliac disease" should lead to a careful review of the diagnosis. The test is also of use in excluding chronic pancreatitis as a cause of diarrhoea for a low excretion is improbable in pancreatic disorders.

In general, d.xylose excretion is associated with disturbance of the intestinal wall of the upper jejunum. It is likely to be normal in the majority of patients with regional enteritis. The folic acid excretion test gives essentially similar diagnostic information. Two patients with adult coeliac disease had normal xylose excretion tests but abnormal folic acid excretions. In one patient with megaloblastic anaemia of pregnancy, the xylose excretion was abnormal when the folic acid excretion was normal. Butterworth *et al.* (1959) found abnormal tests in two patients out of nine. d.Xylose excretion in pregnancy, however, needs further investigation before the significance of low results in anaemia of pregnancy can be fully determined.

## Summary

The five-hour urinary excretion of d.xylose in 35 normal subjects aged 20-62 was found to be 7·2 g. (S.E. 0·27). There was a progressive diminution in excretion in older age groups so that over the age of 65 excretion values below 4·2 g. were of little diagnostic significance.

The findings of d.xylose excretion less than 4·2 g. in patients suspected of pancreatitis with steatorrhoea, of pernicious anaemia, or of normal values in patients suspected to be suffering from adult coeliac disease or tropical sprue should cause their diagnoses to be more carefully evaluated.

In any patient who is not pregnant, the finding of a low xylose excretion in this test should indicate involvement of the jejunum.

No particular diagnostic merit can be attached to the test in regional enteritis, ulcerative colitis, cirrhosis of the liver, or post-gastrectomy syndromes.

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# MULTIPLE ENDOCRINE ADENOMA SYNDROME*

BY

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The case history of a 40-year-old woman with a fatal haemorrhage from a duodenal ulcer, jejunitis, renal lithiasis, hypertrophy of the adrenal glands, multiple adenomas of the pancreas, and three adenomas of both the parathyroid and pituitary glands is reported. Though there was histological evidence, in the bones, of hyperparathyroidism, the serum levels of calcium, phosphorus, and phosphatase and the urinary excretion of calcium were normal.

The significance of low calcium and high phosphorus excretion in the urine as an indication of parathyroid disorder is discussed.

"Multiple endocrine adenoma syndrome" is suggested as the appropriate designation for the clinical disorders in which adenomas of one or more endocrine glands are associated with disorders of the alimentary tract when patients present with recurrent peptic ulceration, pancreatic dysfunction, or watery diarrhoea.

During the past 20 years there have been an increasing number of reports of the occurrence of adenomas of one or more of the endocrine glands and disturbances of the alimentary tract. Reviews of the reported patients have been made, amongst others, by Moldawer, Nardi, and Raker (1954), Ellison (1956), and Donaldson, Vom Eigen, and Dwight (1957). In general, the clinical manifestations present in three ways, gastric hypersecretion and recurrent peptic ulceration often in unusual sites, pancreatitis and pancreatic lithiasis, and persistent watery diarrhoea. The group presenting with peptic ulceration has perhaps gained most prominence as the Zollinger-Ellison syndrome of a non-insulin secreting adenoma of the pancreas and recurrent peptic ulceration. The anatomical findings, however, in all three clinical groups overlap to a considerable extent and the presence of adenomas in many endocrine glands is common. Few patients have been diagnosed accurately during life even with surgical exploration of the abdomen.

The following case report emphasizes the diagnostic difficulties and afforded an opportunity to review our methods of diagnosis with particular reference to the presence of a parathyroid adenoma.

## Case Report

Mrs. J., aged 38, was first seen on July 27, 1956, on account of loss of weight and a recent attack of renal colic. Though she had had an episode of severe epigastric pain 10 years previously, she had been well until two years previously when she had begun to pass two loose stools daily. About the same time, she had had her first attack of renal colic; in all she had four such episodes of renal colic during the next two years. Six months previously, after her second pregnancy, her stools had become more frequent—five or six times a day—pale and often watery. During these two years, she had lost 22 lb. in weight. Physical examination showed no significant features beyond mild finger clubbing. Her blood pressure was 120/80 mm. Hg. Investigations showed marked proteinuria and a heavy urinary infection with *B. proteus*. An intravenous pyelogram was normal but there were a number of calcified opacities anterior and in the region of the tail of the pancreas. A glucose tolerance test showed a fasting blood sugar level of 75 mg./100 ml. rising to 215 mg. at 30 min. and returning to fasting levels in two hours. A diagnosis of chronic pyelonephritis and chronic pancreatitis with probable pancreatic lithiasis was made. The urinary infection responded to antibiotic therapy and the diarrhoea was controlled with pancreatin. The patient was seen regularly. She continued, however, to lose weight and suffered two severe attacks of epigastric pain radiating through between the shoulder blades. She vomited on a number of occasions and epigastric discomfort became more persistent, necessitating admission to hospital for further investigation.

First Hospital Admission.—The patient was first admitted on July 12, 1957. The physical findings were unchanged. Investigations revealed a normal blood count: R.B.C.s $5{\cdot}3 \times 10^6$, haemoglobin 15·9 g.%, W.B.C.s 11,500 with P.C.V. 48% and M.C.V. 89 c.u.,

* Presented at the annual meeting of the British Society of Gastroenterology on November 6, 1959, at Belfast.

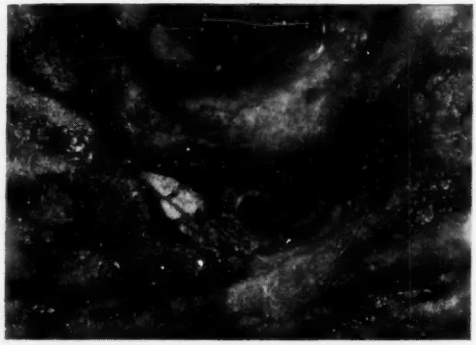

FIG. 1.—*Large transverse ulcer of the duodenum. The nodule above the ulcer is the invaginated duodenal stump.*

FIG. 2.—*Posterior aspect of upper oesophagus, the trachea and larynx showing thyroid (unshaded) and three parathyroid adenomas (shaded).*

M.C.H.C. 33%. The blood urea level was 29 mg./100 ml.; sodium 142, potassium 4·0, chloride 110, and $CO_2$ 26·5 mEq./litre; albumin 3·4 g./100 ml., globulin 2·1 g./100 ml., calcium 10·6 mg./100 ml., phosphorus 2·8 mg./100 ml., and alkaline phosphatase 12 units. Serum amylase was 144 units. Faecal fat excretion over 19 days averaged 19 g. per day, varying from 9·4 to 30·6 g. *X*-ray examination of the stomach and small intestine revealed an excess of resting juice and coarse, widened folds in the duodenum and jejunum. An intravenous pyelogram showed a staghorn calculus in the left kidney. *X*-ray examination of the skull and pituitary fossa was normal. Questionable demineralization of the thoracic and lumbar spine was reported. Radiology of the hands was normal.

Four determinations of the serum calcium varied between 10·1 and 10·6 mg./100 ml. and that of phosphorus between 2·3 and 3·6 mg. per 100 ml. A tentative diagnosis of hyperparathyroidism, chronic pancreatitis, chronic jejunitis, and renal lithiasis was made. Balance studies after a preliminary period of one week on a diet containing 125 mg. calcium and 603 mg. phosphorus per day revealed over six days a daily urinary excretion of 75 mg. calcium and 660 mg. phosphorus per day. Faecal fat excretion during this period was 19 g. per day. In view of the low urinary calcium excretion and levels of serum calcium and phosphorus which were not obviously abnormal, the diagnosis of hyperparathyroidism was considered to be ill founded. She was discharged, taking antacids, pancreatin, and probanthine, to be reviewed frequently as an out-patient. She remained well for four months but the epigastric pain returned, radiating through to the back, relieved occasionally by food or alkalis; it was much worse at night. Admission was arranged in order to carry out an exploratory laparotomy to exclude a pancreatic adenoma.

SECOND HOSPITAL ADMISSION.—This was on February 28, 1958. Physical examination revealed no new features except increased clubbing of the fingers and toes. The blood count was $4{\cdot}19 \times 10^6$ red cells, 12·3 g.% Hb, and 15,600 leucocytes (11,500 polymorphonuclears). The day after admission she vomited 200 ml. blood and despite blood transfusions continued to show signs of intestinal haemorrhage. Laparotomy was carried out on March 3, 1958. The body and tail of the pancreas were macroscopically normal. In the second part of the duodenum was a large ulcer on the posterior wall and several "glands" behind the head of the pancreas. The wall of the duodenum and jejunum was thickened with induration and inflammation of the upper jejunum. It proved impossible to ligate the bleeding point directly, and the pylorus, therefore, was divided and occluded with a gastrojejunostomy below the level of the affected bowel. The operation was temporarily successful in controlling the haemorrhage, but 36 hours later she collapsed and, despite transfusion with 13 pints of blood, she continued to have haematemesis and melaena. She died on March 6.

Post-mortem examination showed no abnormality in the heart or lungs. There was a large transverse ulcer, 5 cm. × 2 cm., about 4 cm. proximal to the ampulla of

FIG. 3

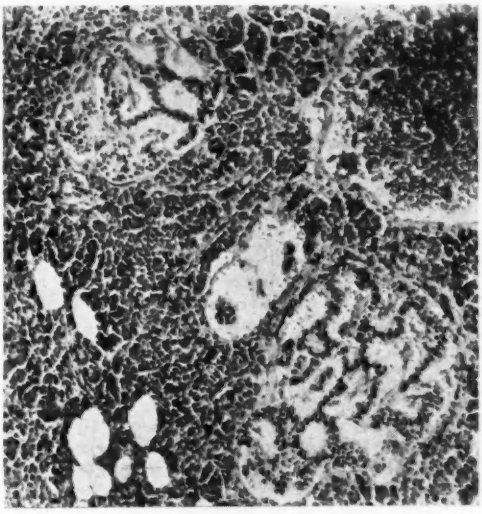

FIG. 5

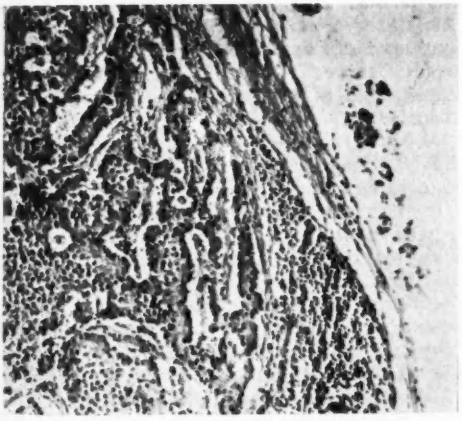

FIG. 4

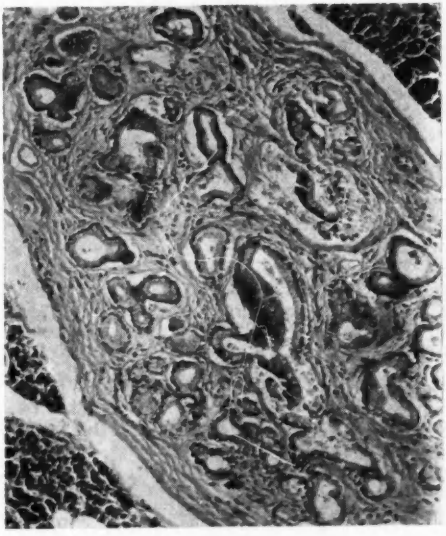

FIG. 6

FIG. 3.—*Bone showing two areas of osteoclastic absorption and early fibrosis. Haematoxylin and eosin* × 150.

FIG. 4.—*Tumour behind the head of the pancreas. An islet tumour with surrounding? remnant of lymph node. Haematoxylin and eosin* × 100.

FIG. 5.—*Two small islet adenomas. Haematoxylin and eosin* × 100.

FIG. 6.—*Pancreatic duct showing marked hyperplasia with many newly formed small ducts. Haematoxylin and eosin* × 100.

Vater with blood clot firmly adherent to the base (Fig. 1). The mucosa of the stomach, despite great distension with blood, showed thickening and mammillation. In the ileum, there were several areas of slight narrowing with some fibrous thickening of the periteoneum; the mucosa was normal. The pancreas appeared normal in size and appearance but there was a tumour, 2 × 3 cm., behind and lateral to the duodenum adjacent to the head of the pancreas. The liver showed mild fatty change. The left kidney contained a large staghorn calculus. The thyroid gland was normal. Three parathyroid tumours, 2 × 1, 1·5 × 0·3, and 2·5 × 1 × 0·5 cm., in size (Fig. 2) were identified. The suprarenals showed moderate diffuse hyperplasia (21g.). The pituitary was macroscopically normal. The skeleton was not obviously softened

HISTOLOGY.—All bones examined showed small areas of osteoclastic reabsorption and fibrosis (Fig. 3) with a few areas of striking intratrabecular reabsorption. Three parathyroids consisted of clear cells with small areas of oxyphil cells and were adenomata with normal glands attached to each. The pituitary (examined completely by serial sections) contained three microscopic chromophobe adenomata with varying amounts of hyaline stroma. The ulcer of the duodenum was eroding the muscle coats and penetrating the pancreas. The small intestine showed mild non-specific chronic inflammation. The adrenals showed a thickened hyperplastic cortex containing a large amount of sudanophil birefringent fat. The tumour adjacent to the head of the pancreas was a large islet tumour apparently involving a lymph node (Fig. 4). Of the 14 blocks cut through the pancreas only three were normal. Numerous small islet tumours of varying sizes were present in the remainder (Fig. 5) with differing degrees of fibrous atrophy, ductal proliferation (Fig. 6), and dilatation.

## COMMENT

The finding of an abnormal gastric mucosa recalls the observation of Kenney, Dockerty, and Waugh (1954) that 10-15% of patients with giant rugae have endocrine adenomas. The finding of multiple adenomas in the pancreas was disquieting since it had been examined specifically with this possibility in mind both at laparotomy and at necropsy and pronounced macroscopically normal by two experienced workers.

The extrapancreatic tumour was thought to be a lymph gland at operation and was so confirmed at necropsy though it was completely replaced by tumour tissue. A somewhat similar difficulty was noted by Zubrod (1958).

Renal lithiasis, pancreatic dysfunction, and jejunitis caused us to suspect the presence of a parathyroid adenoma, but the significance of the gastric hypersecretion shown radiologically and jejunitis did not lead the diagnosis of pancreatic adenoma to be seriously considered until the investigations for hyperparathyroidism were apparently indecisive. The presence, therefore, of three large parathyroid adenomas with little evidence of bone disorder or upset blood chemistry was surprising. In particular the low urinary excretion of calcium was unexpected, though Gross (1958) has recorded a similar low calcium output in a patient with a parathyroid adenoma and pancreatic lithiasis.

Reviewing the calcium and phosphorus balances carried out at this hospital on a calcium intake of 125 mg./day and phosphorus of 620 mg./day showed that the increased phosphorus urinary excretion above 550 mg. may have diagnostic significance. Amongst the patients studied were four patients with pancreatic lithiasis, three of whom had marked steatorrhoea. Two of these had had a parathyroid adenoma removed; one had completely normal excretions, but in the other phosphorus excretion was 550 mg./24 hr. The third had no steatorrhoea but normal calcium and phosphorus urinary excretions. The fourth, a man aged 45, had had pancreatic lithiasis since the age of 30, renal lithiasis for five years, diabetes for three, radiological evidence of jejunitis and normal calcium, phosphorus, and phosphatase values in the blood. The urinary calcium and phosphorus excretions were essentially similar to those found in the patient reported above (Ca 69 mg./24 hr., P 740 mg./24 hr.). Exploration of the parathyroids revealed an adenoma.

Accurate balance studies are time consuming and difficult. In our experience, the results of calcium infusion tests and the determination of the creatinine-phosphorus excretion ratios have not been helpful. Preliminary observations suggest that measurement of the diffusible calcium in the serum may be of value. In a further patient, a man aged 54, with pancreatic adenoma, severe diarrhoea and gastric hypersecretion and with normal calcium and phosphorus values in the serum, the diffusible calcium was significantly raised at 6·9 mg./100 ml. of ultrafiltrate, a finding of diagnostic significance for hyperparathyroidism according to Lloyd and Rose (1958).

## DISCUSSION

This case throws little light on the aetiology of the peptic ulceration and adenoma formation but it does underline the likelihood that more than one endocrine gland is involved when a patient presents with recurrent peptic ulceration, pancreatic dysfunction, or watery diarrhoea. The multiple endocrine adenoma syndrome would, therefore, seem to be an apt diagnostic label for all this group. As to the aetiology of the syndrome, it seems unlikely that it is dependent upon a primary pituitary

upset since at present there is no proven pancreatic or parathyroid tropic hormone of the pituitary. Wermer (1954, 1958) postulates that some factor, presumably chemical, which is responsible for the orderly development of the pituitary, parathyroids, and pancreas at an early stage of embryonic life, is absent. A tendency to familial incidence in some of the reported examples is in favour of such speculation. It is evident that much remains to be learnt about these conditions but it is to be hoped they may provide some new clue as to the causation of some common disorders of the alimentary tract.

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# VOLVULUS OF THE SMALL INTESTINE IN ADULTS

BY

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Five cases of volvulus of varying lengths of the small intestine are described. The incidence and the aetiology of the condition are briefly discussed.

Shock as a feature of extensive volvulus is stressed, and its cause in these cases is related to the previous animal experimental work of others. The other clinical features are briefly described.

In the management of these cases the urgency for laparotomy is stressed and immediate delivery from the abdomen of the whole small bowel is advocated. Reference is made to the literature of massive resection of the small intestine to illustrate that the prognosis is not necessarily poor when resections are extensive.

Acute volvulus of the small intestine is one of the most serious abdominal emergencies. Diagnosis may be difficult and delay in operative intervention can be disastrous. When the whole or a major portion of the small bowel mesentery is twisted the patient may deteriorate with alarming rapidity.

The main purpose of this paper is to show how the clinical picture may be expected to vary and to emphasize the importance of "shock" in massive volvulus. Not only is it of interest to correlate the shock seen in some of these cases with the experimental work of others (Aird, 1937; Scott, 1938) but an understanding of the factors involved should lead to rational treatment.

## Case Reports

Case 1.—A man, aged 47, who had undergone a Polya gastrectomy three years previously for duodenal ulcer was admitted on October 14, 1957, complaining of colicky upper abdominal pain of eight hours' duration. Four hours before admission he passed a normal motion and then felt faint. He took a hot drink and then vomited several times. On admission when seen by the house surgeon he was pale, cold and clammy, with a poor pulse volume and a blood pressure of 90/60 mm. Hg. Twenty minutes later when I saw him he had a warm periphery, no pallor, and a blood pressure of 120/80 mm. Hg. There was tenderness in the upper abdomen and a suggestion of central abdominal distension. A straight radiograph of the abdomen showed a few dilated small bowel loops with fluid levels. Another period of shock was then observed and an intravenous saline infusion was started in preparation for laparotomy.

Under general anaesthesia the abdomen was explored through an upper left paramedian incision. A volvulus of the whole small bowel was found, the mesentery being twisted anticlockwise about 180°. The twist was quite loose, causing only slight venous congestion in the mesentery. The small intestine was moderately distended throughout its length. The previous gastrectomy appeared in good order and there were no adhesions to the small intestine. After delivering the small bowel from the abdomen the only apparent abnormality was that the root of the mesentery had a rather short attachment to the posterior abdominal wall. An attempt to lengthen this attachment was made by suturing the terminal ileum below the caecum to the posterior parietal peritoneum and stitching the upper jejunal mesentery to the posterior abdominal wall medial to the descending colon. The post-operative course was uneventful and the patient was well three months later.

Case 2.—A woman of 50 was admitted on December 29, 1957, with a history of severe central abdominal pain radiating into the back for 16 hours. The pain was intermittent and colicky at first but became continuous. She had vomited a small amount of green fluid three times. She had a bowel action soon after the onset of the pain but had not passed faeces or flatus since.

She said that for two months before admission her abdomen had been swelling periodically. She would sometimes bend forward and feel her stomach "roll over". This would be followed by distension and heaviness and was relieved by the passing of flatus.

On examination she was pale and the periphery was cold but not blue. Her blood pressure was 90/60 mm. Hg. The lower abdomen was distended, and a soft mass, which was dull to percussion, appeared to rise out of the pelvis and to reach a point just above the umbilicus. Although the whole abdomen was tender the maximal tenderness occurred over the lower abdominal mass; no peristaltic sounds were heard. It was at first thought that this was a case of twisted ovarian tumour probably with rupture and haemorrhage. When the haemoglobin was reported as 130% reconsideration of the clinical

picture led to a diagnosis of strangulating small bowel obstruction.

The stomach was emptied with a gastric tube and an intravenous saline infusion started. The abdomen was explored under general anaesthesia through a right paramedian incision within an hour of admission. As the incision was being made the anaesthetist reported serious deterioration in the patient whose pulse was barely palpable. A second intravenous drip was then started through which blood was given. On opening the abdomen the whole small bowel was seen to be distended and congested. It was all immediately delivered from the abdomen and a volvulus of the whole small bowel on its mesentery was seen. The colour changes in the distal half of the small gut were fairly advanced, and it was with considerable relief that the colour of the bowel was seen to improve on untwisting the mesentery. A small linear area of doubtful viability where the terminal ileum had been stretched over the twisted mesentery was buried with a Lembert suture. The small intestine was returned to the abdomen all clearly viable. By the time the incision was closed the patient's condition was good, the pulse was of good volume, and the blood pressure almost normal. By the end of the operation the patient had received 1 litre of saline and 300 ml. of blood.

Intravenous therapy and gastric suction were continued for 72 hours. Thereafter, apart from slight abdominal distension which took a week to subside, convalescence was uneventful.

CASE 3.—A man aged 38 was admitted as an emergency on August 30, 1958. For some years he had passed frequent loose stools. He had been investigated elsewhere and labelled as a case of mild colitis.

Forty-eight hours before admission he developed epigastric pain. After a night's rest he felt well enough to go to work but during the day the pain returned and grew more severe. During the 24 hours before admission he had severe, piercing epigastric pain radiating through to the back. The pain was made worse by movement. He vomited some green fluid just before admission and about half a litre of bright red blood after admission. Some hours earlier he had passed some loose stools and flatus.

On examination he was pale with a cold periphery and a pulse of poor volume. His blood pressure was 90/60 mm. Hg. The abdomen was tender and rigid. The upper abdomen was most rigid. No peristaltic sounds were heard. During the next two hours he received 1 litre of plasma, 1½ litres of blood, and 1 litre of saline. His general condition was then sufficiently improved for laparotomy.

The abdomen was explored under general anaesthesia through an upper median incision. A volvulus of the jejunum was found without any apparent causative factor. The oedematous mesentery was tightly twisted clockwise, and 7 ft. of bowel was devitalized with a sharp line of demarcation at each end. The gangrenous gut was resected and an end-to-end anastomosis of bowel with a vigorous blood supply performed 4 in. below the duodeno-jejunal flexure. One further litre of blood and half a litre of plasma were given during the operation.

Post-operatively the patient progressed satisfactorily until the third post-operative day when his pulse began to rise and he rapidly became shocked. The abdomen was found to be tender with some rigidity and rebound tenderness on the left side.

A litre of plasma was given and the abdomen was again explored under general anaesthesia. A further 4 ft. of small bowel immediately distal to the anastomosis was found to be gangrenous, due to thrombosis in the small peripheral mesenteric veins. Again resection and end-to-end anastomosis were performed, leaving about 4 ft. of terminal ileum and 3 in. of proximal jejunum. He received half a litre each of blood and plasma during operation and his immediate post-operative condition was quite good. In view of the mesenteric thrombosis found at the second operation, heparin, 12,000 units six hourly, was given intravenously for four days. By the fourth day after the second operation he had developed extensive collapse of the left lower lobe with areas of consolidation. The clinical course was stormy for 10 days with high fever and mental confusion. The infection slowly resolved with the assistance of physiotherapy, erythromycin, and chloramphenicol. The patient's alimentary canal gave remarkably little trouble, and at the time of his discharge four weeks after admission he was taking a normal diet and passing two or three loose stools a day. Three months later he had gained a stone in weight, he was having two bowel actions a day, and examination of the stool showed no steatorrhoea. The blood electrolytes were normal. He remains well six months later.

CASE 4.—A man of 67 was admitted on April 30, 1958, with a 12-hour history of colicky central abdominal pain of sudden onset. He had not vomited but he could not recollect passing flatus since the onset of the pain.

For the past 30 years he had suffered slight epigastric pain related to food and relieved by alkalis.

He was a fit man in good general condition. There was very slight central abdominal distension but no localized or rebound tenderness. A freely reducible right inguinal hernia appeared to be an incidental finding.

An hour after admission the abdomen was explored through a right paramedian incision under general anaesthesia. The small bowel was moderately distended and some straw-coloured free fluid was found. A volvulus of a short loop of ileum had occurred, at the apex of which lay a large multilobular subserous lipoma. The volvulus was not a tight one and although the lumen had been obstructed by it the blood supply of the loop was not yet affected. Ten centimetres of ileum bearing the lipoma were resected and an end-to-end anastomosis performed.

The post-operative course was smooth.

CASE 5.—A man of 48 was admitted on March 19, 1958, with a history of constant upper abdominal pain with colicky exacerbations lasting three hours. He had vomited green fluid three times. Eight years previously he had undergone a Billroth I partial gastrectomy for duodenal ulcer.

He was a well-built man whose general condition was

good. He was rolling about with spasms of pain. There was slight upper abdominal distension and generalized abdominal tenderness with guarding in the upper abdomen. Peristaltic sounds were markedly increased.

Acute upper small bowel obstruction was disgnosed and immediate laparotomy arranged. The abdomen was opened under general anaesthesis through the old scar. Four to five feet of upper jejunum was distended and the mesentery of the distended segment was twisted. The apex of the twisted loop was adherent to the old wound. The adhesion was divided and the loop untwisted; its blood supply was not impaired. A few small bowel adhesions were severed and the abdomen closed.

He developed a silent abdominal distension post-operatively and he did not pass flatus for four days. Thereafter convalescence was smooth.

## Discussion

INCIDENCE.—No one person is likely to see very many of these cases and unfamiliarity with a variable clinical picture probably still contributes to a considerable mortality. McKechnie and Priestley (1936) found only 37 cases in reviewing the condition over 25 years at the Mayo Clinic, and Moretz and Morton (1950) found 36 cases in 22 years at the University of Rochester.

AETIOLOGY.—In most published series of volvulus of the small bowel the majority of cases show some definite aetiological factor. Congenital malrotation and congenital or post-operative adhesions are the commonest causes. Tumours, as in Case 4, are occasionally responsible and primary mesenteric vascular occlusion is sometimes blamed. In Cases 1 and 2, in which the volvulus was total, and in Case 3, in which the volvulus was subtotal, no definite predisposing cause was found. Case 1 appeared to have a mesentery which was long in relation to the length of attachment of its root. Kerr and Kirkaldy-Willis (1946) describe seven cases of total small bowel volvulus in East Africans in whom volvulus is a relatively common cause of obstruction of the small bowel. They suggested that the racial dietary habit of taking large quantities of maize gruel at one time might load the small intestine and initiate volvulus. The small bowel might become loaded very quickly more easily in a patient, such as Case 1, who had been subjected to a gastrectomy. The history of this case shows nothing to support this supposition.

Cases 2 and 3 were too critically ill to justify a prolonged search for possible causative factors.

SHOCK.—In cases where the volvulus involves the whole or a large part of the small intestine, "shock", as in Cases 1, 2, and 3, is a prominent feature. It is not necessarily a late sign. When the whole or a substantial portion of the small bowel mesentery becomes twisted the venous return soon becomes obstructed. Aird (1937) showed experimentally that the maximum loss of whole blood in intestinal strangulation occurred with pure venous occlusion. He showed that 50% of the blood volume could be lost into the splanchnic bed. The episodes of hypotension, pallor, and sweating in Case 1 are adequately explained if the twist of the whole mesentery was a slight one, the veins becoming temporarily obstructed and relieved by spontaneous partial untwisting of the volvulus. The operative finding of a loosely twisted mesentery, minimal congestion of the gut, and minimal peritoneal exudation supports this explanation.

Scott (1938) made a detailed study of the shock-producing factor in experimentally produced intestinal strangulation in dogs. He found that, if the venous return alone were occluded in a closed loop obstruction, death occurred earlier than in pure arterial or complete arterial and venous occlusion. In pure venous occlusion 60% of the animal's blood volume was lost into the lumen, bowel wall, and coelomic cavity. In pure arterial occlusion transudation of plasma into the peritoneal cavity as a response to the presence of a necrotic segment of bowel was the most important shock-producing factor. It is to be expected, therefore, that some cases of volvulus of the small bowel will become shocked first from blood loss as a result of venous occlusion and later from protein and fluid exudation. This combination is illustrated in Case 2. The patient's very rapid recovery during the short operation can be explained by the return to the general circulation of a large volume of blood in the congested mesenteric veins on untwisting the volvulus. The small amount of fluid and blood given intravenously during operation could hardly explain such a dramatic and rapid recovery. The twice-checked haemoglobin of 120% in this case illustrates that a great amount of protein and fluid as well as blood is lost.

Scott also showed that absorption of bacterial toxins from the peritoneal cavity as a shock-producing factor was a late phenomenon occurring after the gut wall had become necrotic. Even in Case 3 this stage had not been reached, since the shock state was reversed as soon as the estimated blood and fluid loss had been replaced.

PAIN.—This is usually severe and gripping in character but often continuous. Pain is usually the dominant symptom in small loop volvulus and, as in Case 4, it may be the only definite clinical feature.

VOMITING.—Vomiting may be absent or slight in a case which urgently needs laparotomy. Evans and Bigger (1947) say that vomiting is usually incessant

in strangulating obstruction but Kerr and Kirkaldy-Willis (1946) describe six cases of small-bowel volvulus in which vomiting was not a marked feature. It is clear that incessant vomiting is not necessarily a symptom. Blood may be vomited, as in Case 3, when venous obstruction in the mesentery precedes occlusion of the lumen of the proximal limb of the volvulus.

BOWELS.—The patient, as in Case 2, may have one or more bowel actions after the onset of the pain. Blood may be passed if the lumen of the distal limb of the volvulus is incompletely occluded. Usually complete constipation to faeces and flatus follows; its significance may not be great if the history is short.

ABDOMINAL PHYSICAL SIGNS.—Obvious distension was present in Case 2 only. The diagnosis must often be made in its absence. Tenderness may be slight when there is minimal congestion of the bowel (Case 1), or gross and accompanied by rigidity, as in Case 3, when bowel is devitalized. Peristaltic sounds may be absent (Cases 2 and 3), diminished (Case 1), normal (Case 4), or increased (Case 5). Smith (1945) suggests that colic associated with absent bowel sounds is typical of strangulation, and Evans and Bigger (1947) say that the sounds are diminished in frequency and lower in pitch in strangulating obstruction. The behaviour of peristaltic sounds appears to vary with the amount of mesentery twisted and the degree of vascular impairment of the bowel.

MANAGEMENT.—The exact diagnosis may not be made pre-operatively but it is usually possible to decide that a serious abdominal disaster has occurred. Moretz and Morton (1950) say that the chief problem is differentiation between an obstruction needing surgery and one which can be treated conservatively. This problem disappears when it is accepted that, with the occasional exception of the much-scarred abdomen, all cases of acute small intestinal obstruction require laparotomy (Cooke, 1958) since it is impossible to differentiate certainly between occlusion and strangulation.

In cases of massive volvulus the circulatory volume must be restored with blood and plasma pre-operatively. Much is to be gained by the earliest possible operative intervention; in Case 2 a resection of gut of some magnitude might have been necessary if too complete a resuscitation had been attempted, although perhaps we erred on the side of haste in opening this abdomen. Provided the patient is made fit for general anaesthesia further resuscitation and operation can be synchronous. Much unnecessary delay can be avoided in the operative diagnosis by immediate delivery of the whole small gut from the abdomen (Barbosa, 1944). In extensive volvulus, it is in any case necessary to deliver the small intestine into the abdomen in order to untwist the mesentery. When there are many dilated small bowel loops, attempts at finding the obstructing lesion while keeping the bowel in the abdomen are fruitless, and volvulus may even be completely overlooked (Woods, 1945).

There is no alternative to massive resection when the bowel is gangrenous as in Case 3. More of these cases are probably surviving the immediate post-operative period as a result of proper blood and plasma replacement. It is some comfort to the surgeon to know that very short lengths of small intestine may be compatible with life. Several instances of survival with only 7 or 8 in. of small bowel are recorded (Bothe, Magee, and Driscoll, 1954; Wilkie, 1950; Jackson, Linder, and Berman, 1951; Brezin and Oren, 1954), but the majority with very short lengths exhibit nutritional deficiencies. The subject is thoroughly reviewed by Pullan (1959). Some evidence is accumulating that when a reasonable segment of ileum can be preserved the prognosis, particularly with regard to fat absorption, is improved (Pullan, 1959; Pietz, 1956). Croot (1952) points out that for anatomical reasons distal resections are more common, and few cases are recorded where virtually all the jejunum was resected and a few feet of ileum preserved. Littlefield (1919) records a patient with 4 ft. of distal ileum in good health three months later, and McClenahan and Fisher (1950) describe a man who was remarkably well after 18 months with only 1 to 2 ft. of ileum and no jejunum. Case 3 in this series is a further example of a patient subjected to a massive resection of proximal small bowel in good health after nine months.

The prevention of recurrence of volvulus offers no problem when a definite cause is found and removed (Cases 4 and 5) or an extensive resection performed (Case 3). In Case 1 a procedure designed to lengthen the root of the mesentery was attempted, but, like Barbosa (1944), I have doubts about its value. In Case 2 the patient's condition precluded all but life-saving measures, but probably such grossly affected bowel becomes sufficiently adherent to prevent recurrence. Recurrent massive volvulus may justify a Noble plication (Noble, 1937).

Post-operatively the possibility of spreading thrombosis occurring in the mesentery must be kept in mind. Deterioration in the condition of a patient, such as in Case 3, is easily overlooked in the immediate post-operative period. It must also be remembered that considerable quantities of protein and fluid may be lost into the bowel wall and into

the peritoneal cavity after operative relief of an extensive volvulus and generous intravenous replacement of protein and fluid may be needed.

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# ANNUAL MEETING OF THE BRITISH SOCIETY OF GASTROENTEROLOGY

The 1959 meeting of the Society was held in Belfast on November 6 and 7 with Professor H. W. Rodgers as President and Professor R. B. Welbourn as the local secretary. It was a notable meeting on account of the number of important decisions taken in relation to the Society's affairs, also for the excellence of the scientific communications and the high standard of discussion.

It was decided that the time had come for the size of the Society to be increased. Honorary members should be increased from five to 10, ordinary membership should be increased from 65 to 100, and no definite limit should be placed on the number of associate members who should be elected from younger physicians, surgeons, and others engaged in research or interested in gastrointestinal problems.

The second major decision was to publish a journal to be entitled *Gut* (The Journal of the British Society of Gastroenterology). Arrangements had been made with the British Medical Association to enable this to be published as one of their specialist journals.

The following were elected as full members: Alan Hunt, William Burnett, T. J. Butler, T. S. Heslop, Douglas Clark, Peter Ingram, A. Elliott Smith, Nelson Coghill, W. T. Irvine, B. C. Morson, T. L. Kennedy, and H. Daintree Johnson.

New associated members elected were: C. C. Booth, D. A. W. Edwards, A. M. Connell, Margot Shiner, J. A. C. Wilson, A. M. Dawson, K. Bredon Taylor, J. E. Lennard-Jones, D. B. Feather, James Kyle, A. E. Read, Michael Atkinson, and J. K. Wagstaff.

The annual dinner was held at Queen's University, and afterwards travel photographs were shown.

On the Saturday afternoon after the meeting a fine selection of clinical rarities was presented by the staff of the hospital.

## SCIENTIFIC MEETING

### Early Diagnosis of the Cause of Haematemesis

G. N. Chandler reported 102 patients admitted as emergencies for haematemesis and melaena who had been studied in the acute stage of the illness by a combination of special investigations. Immediate gastric intubation, with overnight hourly *p*H estimations, was followed by gastroscopy the next morning and in the afternoon a barium meal was given in the ward and radiographs taken. In a high proportion of patients (80%) a correct early diagnosis was achieved by these combined procedures, which proved to be safe, informative, and helpful in the management of the individual patient. (This paper is published in full on page 6.)

During the brisk discussion that followed Watkinson confirmed the value of early barium meal examination in the ward. Norman Tanner stressed the value of gastroscopy and pointed out that the finding of atrophy of the gastric mucosa was important evidence against a duodenal ulcer being present, and underlined the usefulness of the extra information which can be obtained by distending the fundus with air and then slowly withdrawing the gastroscope; this may enable the presence of a hiatus hernia, varices, or a linear laceration (Mallory-Weiss syndrome) to be detected. Ihre stated that provided the blood volume was restored by blood transfusion it was perfectly safe for the patient to be radiographed in a standing position.

### Choledochoscopy

A. Nicholson reported on 148 examinations made with a special endoscope designed for looking up the common bile duct. Views were shown of the ampullary region at one end and the hepatic ducts at the other. The technique had been of value in demonstrating the presence of stones and cholangitis. No peristaltic activity had been noted.

### Clinical and Laboratory Considerations in the Treatment of Chronic Pancreatic Disease

O. Fitzgerald, P. Fitzgerald, and J. Fennelly discussed the combination of upper abdominal pain with acute exacerbations and fat intolerance, and it was noted that 15% of the patients had had evidence of jaundice not always with stone; unlike the American series only 5% had been alcoholics. Vitamin A absorption was decreased and this might help in diagnosis. With the secretin pancreozymin test confirmatory evidence was found in 60% but both false positive and false negative results were sometimes recorded. Stenosis of the sphincter of Oddi was an important factor in some cases, and in one patient, a young neurotic girl, a papilloma in the sphincter had been discovered. Surgical treatment of chronic pancreatitis was discussed and the various possible measures reviewed. It was considered that pancreatectomy was very seldom needed and sphincterotomy had usually been performed.

### Pancreatic Secretion in Response to Food following Gastrectomy

T. J. Butler reported an elegant and painstaking study on intubation tests before and after Billroth I partial gastrectomy. Fifty patients had two tests before and two after operation, as follows: (*a*) Duodenal meal before operation, (*b*) jejunal meal before operation, (*c*) duodenal meal after gastrectomy, (*d*) jejunal meal after gastrectomy. Comparison of (*c*) with (*a*) showed a reduced output of all constituents to two-thirds—three-quarters of pre-operative levels. Comparison of (*d*) with (*b*) indicated the type of response that would occur in Polya patients. After gastrectomy, when food enters the jejunum directly, the pancreas continues to secrete but only at its resting level. This, however, is greater after gastrectomy than before. Comparison of studies of patients with vagotomy alone showed that the modification of the pancreatic response seen after gastrectomy is related to the co-incident vagotomy.

During the discussion on these two papers Howat referred to the possibility of codeine being a factor in the production of pancreatitis as it may cause spasm of the sphincter of Oddi. In some cases a background of migraine may lead to the continued use of tab. codeine co.

### Symposium: "Hormones and the Alimentary Tract"

W. B. Henbest, by invitation, gave a most lucid exposition on the chemical background of steroid metabolism. The speaker had thoughtfully provided the audience with photostat copies of a map showing the pathways of steroid metabolism. This was likened to a map of the London underground service with steroid rings taking the place of stations. The chemical inter-relations of bile acids—cholesterol, cortisol, aldosterone, progesterone, and medrone—were demonstrated, and this formed a necessary and most interesting background to the subsequent contributions on steroids.

### The Hormone Excretion during Prolonged A.C.T.H. Adminstration in Patients with Ulcerative Colitis and Entero-colitis

W. Sircus, W. I. Card, J. B. Brown, G. P. Crean, K. Fotherby, and J. A. Loraine reported observations on urinary gonadotrophins, oestrogens, 17-hydroxy-corticosteroids, and 17-oxysteroids during and after A.C.T.H. treatment. While the oestrogen, 17-hydroxy-cortisteroids, and 17-oxysteroids followed a uniform pattern, in so far as the excretion of these hormones rose with treatment and fell to control values on finishing treatment, the gonadotrophin response differed markedly as between patients.

There was no clear-cut correlation between clinical and hormonal findings although the numbers were still small. There was a suggestion that the increase in gonadotrophin and oestrogen excretion might be associated with improvement. It was noted that A.C.T.H. after the menopause had given somewhat better results than before.

During the discussion Sir Charles Dodds noted that aldosterone production was not affected by A.C.T.H. and raised the possibility of different clinical results being associated with different batches of A.C.T.H. Truelove commented that for the M.R.C. trial the same batch had been used throughout.

### The Effects of A.C.T.H. and Corticosteroids on Gastric Secretion in Humans

G. P. Crean had measured the gastric acid secretion in terms of maximal histamine secretion in 18 patients during prolonged treatment with A.C.T.H. and corticosteroids. Gastric secretion was depressed in four, unchanged in three, and increased in five patients treated with A.C.T.H. The secretory changes ranged from complete suppression (in a patient with an initially low secretion) to an increased secretion four times the order of control values. In each of five patients treated with cortisone and in one treated with prednisolone, secretion was increased, the increases ranging from 33% to 160% of control values.

The effects of single intravenous injections and of continuous intravenous infusions of hydrocortisone, and of intravenous infusions of A.C.T.H. on the hydrogen ion and electrolyte content of basal and maximally stimulated secretion were also observed. In these acute experiments the greatest changes were seen in those patients in whom acid secretion had been noted to increase during prolonged steroid therapy. Increased rate of secretion could be due to either increased metabolic activity or to an increase in number of parietal cells. The atrophy of the gastric mucosa associated with adrenal insufficiency was commented upon.

### The Effects of A.C.T.H. and Corticosteroids on Gastric Secretion in the Dog

R. B. Welbourn, S. D. Clarke, and D. W. Neill reported that A.C.T.H., cortisone, medrone (a pure glucocorticoid), and aldosterone all increase the volume and acidity of secretion from Heidenhain pouches under varying conditions. Cortisone increases the maximal secretory capacity in response to histamine. All the substances reduce the concentrations of sodium and potassium in the gastric juice at the same time as they increase the concentration of hydrogen ions. They do not influence the concentration of chloride ions. The concentration of pepsin is reduced. The viscosity of the resting juice is reduced. Histological observations suggested that the number of parietal cells were increased by 50% after cortisone with a reduction in the number of peptic cells.

### The Excretion of 17-Ketosteroids and 17-Hydroxy-corticosteroids in Patients with Active Duodenal Ulcers

C. N. Pulvertaft and A. G. Green had studied 58 male patients with active duodenal ulcers and 36 normal controls. In the ulcer group, the excretion of 17-keto-steroids was found to be within normal limits but the mean excretion of 17-hydroxycorticosteroids tended to be lower than the normal controls; moreover, in ulcer patients the amount of 17-hydroxycorticosteroids appeared to be directly related to the urine volume. In the patients referred for surgery, the excretion of uropepsinogen was also studied in order to evaluate the effect of

gastric resection. The patients were re-examined six months after gastrectomy and the 17-ketosteroids and 17-hydroxycorticosteroids repeated as a routine. It had been found that partial gastrectomy lowered the excretion of uropepsinogen, and also, surprisingly, the 17-ketosteroids (16 patients); it appeared to have a similar effect on 17-hydroxycorticosteroids, though the number (nine) was small.

### Hormone Metabolism and the Liver

S. Shaldon reviewed the rôle of the liver in the inactivation and production of metabolites of hormones. This is achieved by structural modification, conjugation often as a glucuronide or sulphate and excretion into the bile. Most of the steroid hormones undergo an enterohepatic circulation in a similar fashion to bile acids. The effect of chronic liver disease is to reduce detoxification resulting in slow disappearance of hormones from the blood, reduced urinary metabolites, and in some cases increased effects of the hormones on their target organ. It is the mechanism of the hyperoestrogenism in cirrhosis as manifested by skin changes, gynaecomastia, testicular atrophy, and impotence. It accounts also for the increased effects of growth hormones in female juvenile cirrhotics.

### Multiple Adenoma Syndrome

W. T. Cooke, D. I. Fowler, R. Gaddie, E. V. Cox, M. J. Meynell, and D. Brewer presented a case report of a 40-year-old woman with a four-year history of chronic diarrhoea, abdominal pain, and renal lithiasis. Observations over 12 months indicated grosssteatorrhoea (controlled by pancreatin), and normal calcium, phosphorus, and phosphatase values in serum. She excreted daily 40-60 mg. calcium in the urine, on an intake of 125 mg. Radiological evidence of jejunitis and nephro-lithiasis was present. While awaiting laparotomy, she died from uncontrollable haemorrhage from a large ulcer in the second part of the duodenum. Necropsy revealed three pituitary adenomas, three parathyroid adenomas, an islet cell adenoma in the head of the pancreas, and diffuse adenomatosis through the body and tail of the pancreas (macroscopically normal). Histological evidence was there of hyperparathyroidism in the bones, hypertrophied adrenal glands, and duodeno-jejunal ulceration. The metabolic investigation and diagnostic implications were considered with those in three patients with parathyroid tumour and steatorrhoea, two with pancreatic lithiasis, and one with both pancreatic and renal stones.

### Effects of Glucagon on Gastric Secretion

S. D. Clarke, R. B. Welbourn, and D. W. Neill said that work on dogs with Heidenhain and Pavlov pouches indicated that glucagon reduced greatly the antral and nervous phases of gastric secretion and, to a small extent, the resting secretion and that stimulated by histamine. The effect was not a result of the associated hyperglycaemia. It is possible that glucagon plays a part in the physiological control of gastric secretion. It is most unlikely that glucagon is the cause of the gastric hypersecretion in the Zollinger-Ellison syndrome.

### The Liver's Role in Histamine Absorption from the Alimentary Tract

W. T. Irvine presented evidence that, in dogs and man, free histamine is absorbed in small quantities from the small and large bowel and rapidly excreted in the urine.

At physiological dose levels the amounts absorbed did not stimulate secretion of acid in denervated gastric pouches. But after portocaval anastomosis or the use of an anti-histaminase drug, similar doses produced a strong acid response from these pouches. Alternate portal and systemic intravenous infusions of histamine at the same dose rate showed that passage of histamine through the liver reduced both the acid response in the stomach and the output of free histamine in the urine. This histamine-destroying rôle of the liver may be necessary to protect the gastric mucosa from continuous stimulation by histamine absorbed from the bowel, and may account for the higher incidence of peptic ulcer in cirrhosis.

Some doubts were expressed about this process in the ensuing discussion in view of the relative frequency of gastric ulcer in these cases and the association of other factors such as venous congestion.

### The Mode of Action of Gastrin as Examined in the Experimental Animal and its Action via the Release of Histamine in the Stomach Wall

A. N. Smith described studies to find out whether gastrin acted directly on the parietal cells through the intermediate release of histamine. With an almost histamine-free preparation of gastrin it was found: (1) That gastrin had a local action on the parietal cells. (2) That histamine was also released from the stomach wall. Other tissues, however, were found to release an even greater amount of histamine. This was shown by perfusing or incubating the tissues with gastrin. (3) The amount of histamine released from the stomach wall into the portal blood was very small. It could be demonstrated best by temporary diversion of the portal blood via a shunt into the systemic circulation. The resultant fall in the systemic blood pressure was abolished by a histamine antagonist.

It seemed that this was a non-specific release of histamine and in fact much more occurred in other sites of the body. It was noted that the effect of gastrin was dependent on intact vagal innervation.

### A Search for Factors Affecting Gastric Secretion in Thoracic Duct Lymph of Dogs

I. D. A. Johnston reported experimental work studying the inhibitory influence of fat in gastric secretion, especially to find out whether an inhibitory factor could be isolated from fat in the lymph duct. The thoracic ducts of dogs were cannulated, and lymph collected during both stimulation and inhibition of gastric secretion. The lymph samples were tested by injecting them intravenously into dogs with gastric pouches secreting in response to histamine. About half the samples inhibited gastric secretion. The rest either stimulated secretion or had no effect. Reactions occurred in about a third of the animals which had inhibition. Inhibitory

and stimulatory factors were present as often in resting as in any other type of lymph. Lymph collected after a meal of fat was separated into fat and fat-free portions by centrifugation. The fat fractions stimulated gastric secretion while the non-fat fractions carried the inhibitor when it was present. The presence of inhibitory or stimulatory factors in lymph has not been found to correlate consistently with any physiological sequence.

During the discussion it was pointed out by Sircus and Hunt that the amount of oil was an important factor and anything producing nausea would depress secretion.

### Post-vagotomy Diarrhoea

H. Burge gave an account of the anatomy of the vagus nerve with special reference to the hepatic and pyloric branches, and a comparison was made between routine vagotomy and patients who had had a selective vagotomy leaving the hepatic branch. Only one out of 18 such patients had looseness of the bowels compared with 10 out of 25 using the previous technique.

### The Budd-Chiari Syndrome

J. B. Gibson presented a full account of this thrombophlebitic disease which affects the hepatic veins. The patients are often young adults. The onset of symptoms may be gradual or sudden whatever the lesions; extensive obstructions can exist without symptoms. The lesions are thrombotic rather than inflammatory. The existence of ostial sphincters explains the remarkable localization of lesions to the ostia in Chiari's disease. Of 13 cases of this syndrome of hepatic-venous obstruction, without cancer, one is well, another was diagnosed incidentally at necropsy, and 11 were fatal. In three of the last group the large hepatic veins were involved primarily; the ostia were primarily involved (Chiari's disease) in five and probably in three other cases. Liver biopsies may show blood lagoons. It seemed likely that anticoagulants exerted a favourable effect on the course of the disease, and in time recanalization of the clot may occur.

In the discussion Naish reported a puerperal case which had been treated successfully by anticoagulants and Fitzgerald commented on the association with polycythaemia rubra vera.

### Intestinal Pseudo-obstruction with Steatorrhoea

J. Naish and W. M. Capper reported a new syndrome of recurring episodes of pseudo-obstruction associated with hypermotility of the small intestine and diarrhoea. A patient was reported who had had recurrent bouts of abdominal pain with distension and vomiting and was found to have steatorrhoea. Radiographs showed distended small intestine full of gas and fluid that was shuttled back and forth by segmental movements. At laparotomy there was no obstructive lesion but a most remarkable peristaltic activity of the gut was observed. Histology of the jejunum was normal apart from thickened muscular coats.

From the study of another case and of reports of patients sent from colleagues elsewhere it was suggested that a combination of recurrent abdominal distension and vomiting, steatorrhoea, and abnormal peristaltic movements of the small intestine might be associated with the syndrome on its own without being associated with other general or local diseases.

During the discussion Bruce Pearson mentioned the possible value of prostigmine in such patients and Badenoch referred to the possibility of mesenteric vascular insufficiency.

### Manometric Study of Sigmoid Motility in Functional Bowel Disorders

A. M. Connell and E. N. Rowlands, using tiny balloons and a metal capsule optical manometer, studied the motility of the sigmoid colon in health and disease. Patients with active diarrhoea have a diminution of all types of intraluminal pressure changes.

A proportion of patients with non-specific functional bowel disorders had atypical patterns of motility. Evidence was presented that some of these variations possibly represent a failure of the normal neuromuscular control of the large bowel.

### Radiological Examination of the Small Intestine

W. G. Scott-Harden stated that the effective use of the small bowel enema depends upon accurate and immediate duodenal intubation and upon a double contrast enema to overcome the disadvantage of total opacification of the coils with overlay of the critical areas. A method of controlled manipulation of the duodenal tube was described, using a sheathed tube unit with opaque marker rings to ensure accurate positioning during fluoroscopy. The tube and technique of introduction were illustrated. A number of illustrative films were shown.

## SCIENTIFIC DEMONSTRATIONS

The following demonstrations were shown:

### An Abrasive Balloon for Gastric Cytology

*P. A. J. Ball* and *A. H. James* (Cardiff)

This instrument has an abrasive surface which can be infolded during passage and withdrawal so that it is not contaminated with oesophageal cells. This makes examination of the smear less laborious. Our experience suggests that the instrument has its greatest use when the suspected lesion is near the cardia. It is made of polyvinyl chloride tubing and sheeting, welded by high frequency dielectric heating. The abrasive surface is made of nylon net.

### Gastroscopy

*H. W. Rodgers*

The gastroscope and the indications for its use are described. The value of the investigation is illustrated with coloured drawings. The chief danger is perforation of the crico-pharyneal region, which is diagnosed by the presence of fever and local tenderness and treated by surgical exploration.

### References

Rodgers, H. W. (1948). In *British Surgical Practice*, Vol. 3, p. 419. Butterworth, London.
—— (1956). In *Operative Surgery*, ed. C. Rob and R. Smith, Vol. 1, p. 32. Butterworth, London.

### The Nutritional Aspects of Gastric Surgery

*R. B. Welbourn* (1956)

Loss of weight, iron-deficiency anaemia, megaloblastic anaemia, and vitamin B deficiencies are common after operations on the stomach. The factors which influence them and their causes and treatment were described.

#### References

Welbourn, R., Hughes, R., and Wells, C. (1951). *Lancet*, **1**, 939.
—— Nelson, M. G., and Zacharias, F. J. (1956). *Brit. J. Surg.*, **43**, 422.
Wells, C., and Welbourn, R. (1951). *Brit. med. J.*, **1**, 546.

### Treatment of Weight Loss after Partial Gastrectomy

*I. D. A. Johnston, F. K. Acheson*, and *R. B. Welbourn* (1958)

Weight gains, averaging about 4 lb. in eight weeks, are produced in patients who are underweight by dietary supervision, testosterone, or iproniazid. Dummy tablets, iron intramuscularly, and vitamin $B_{12}$ have no effect.

#### Reference

Johnston, I. D. A., Welbourn, R. B., and Acheson, F. K. (1958). *Lancet*, **1**, 1242.

### Gastric Secretions and the Maintenance of Nutrition in the Dog

*I. D. A. Johnston* and *R. B. Welbourn* (1958)

Dogs which have lost their gastric reservoirs, but whose gastric secretions enter the duodenum, maintain weight better than those which have undergone total gastrectomy. This is probably the result of better absorption of fat and nitrogen. There is no evidence of an internal gastric secretion which influences nutrition.

#### Reference

Johnston, I. D. A., and Welbourn, R. B. (1958). *Brit. J. Surg.*, **46**, 163.

### Gastrectomy in the Rat

*I. D. A. Johnston* and *R. B. Welbourn* (1956, revised, 1958)

Total gastrectomy always causes loss of weight, impairment of growth, thickening of oesophageal epithelium, anaemia, and early death. Loss of secretory function is more important than loss of the reservoir function of the stomach. Iron intramuscularly causes temporary increase in weight and correction of anaemia.

### Gastric Secretion and the Pituitary-adrenal Axis

*J. Kyle, D. E. Neill*, and *R. B. Welbourn* (1957)

In the rat adrenalectomy reduces gastric secretion. Cortisone subsequently increases it to a supranormal level. Hypophysectomy greatly reduces secretion. Cortisone and growth hormone restore it. In patients with Cushing's syndrome gastric secretion is increased. Subtotal adrenalectomy restores it to normal.

#### References

Kyle, J., Logan, J. S., Neill, D. W., and Welbourn, R. B. (1956). *Lancet*, **1**, 664.
—— and Welbourn, R. B. (1956). *Brit. J. Surg.*, **44**, 241.

### Effects of Corticotrophin and Adrenal Steroids on the Secretion from Denervated Gastric Pouches in Dogs

*S. D. Clarke, D. W. Neill*, and *R. B. Welbourn* (1959)

The effects of corticotrophin (A.C.T.H.), cortisone, "medrone" (a "pure" glucocorticoid), and aldosterone (a "pure" mineralocorticoid) on gastric secretion from denervated (Heidenhain) pouches in dogs were observed. All increased the volume and acidity of the juice under a variety of conditions. They reduced the sodium and potassium content of the juice, but did not affect the chloride content. The viscosity of the resting juice was reduced. The pepsin content was reduced.

### The Effect of Cortisone on the Maximal Secretory Response of the Stomach to Histamine

*S. D. Clarke, D. W. Neill*, and *R. B. Welbourn* (1959)

Cortisone increases the maximal secretory capacity, in response to histamine, of denervated pouches in dogs.

### The Effect of Glucagon on Gastric Secretion in the Dog

*S. D. Clarke, D. W. Neill*, and *R. B. Welbourn* (1959)

Glucagon reduces the volume and acidity of gastric secretion from innervated and denervated pouches in dogs. The effect is independent of its hyperglycaemic action.

### The Preparation of Gastric Pouches in Dogs

*G. A. Smith, R. B. Welbourn*, and *S. D. Clarke* (1959)

The surgical technique for the preparation of denervated (Heidenhain) and innervated (Pavlov type) pouches was illustrated.

#### Reference

Hollander, F. and Jemerin, E. E. (1938). *Proc. Soc. exp. Biol. (N.Y.)*, **39**, 87.

### Some Observations in a Patient with Zollinger-Ellison's Syndrome

*Margaret T. England, J. M. French, Annette B. Rawson*, and *F. A. R. Stammers* (Birmingham)

### Metabolic Studies in a Patient with Whipple's Disease Diagnosed by Suction Biopsy, with Special Reference to the Control of Diarrhoea with Antibiotics

*Margaret T. England, J. M. French*, and *Annette B. Rawson* (Birmingham)

### Hepatic Disease

*H. W. Rodgers, J. B. Gibson, J. A. McCredie*, and *T. T. Fulton* (1958, revised 1959)

The clinical features were presented, with the modes of onset and the signs and symptoms, of hepatic failure. The special investigations were described, including needle biopsy and special radiological techniques.

Photomicrographs of histological features were demonstrated. An analysis was shown of the causes of 111 cases of hepatic disease.

### Total Arterialization of the Liver

*J. A. McCredie, J. R. Doggart,* and *R. B. Welbourn* (1957)

The effects in dogs of portocaval anastomosis and of the same procedure combined with arterialization of the hepatic and of the portal vein were compared. In normal dogs arterialization prolongs life and maintains weight and hepatic function better than portocaval anastomosis alone, but tends to thrombose the portal vein. Arterialization confers no benefit on dogs with cirrhotic livers.

#### References

McCredie, J. A., Doggart, J. R., and Welbourn, R. B. (1957). *Brit. J. Surg.*, **45**, 83.
Doggart, J. R., McCredie, J. A., and Welbourn, R. B. (1958). *Vet. Rec.*, **70**, 279.

### Peritoneoscopy

*H. W. Rodgers* and *J. A. McCredie*

The chief indication for peritoneoscopy is in the investigation of the condition of the liver. It is also useful in providing information on other abdominal organs and tumours that can be seen lying anterior to or level with the great omentum, and for inspecting the pelvis. The technique and dangers were shown and some examples of the appearances were illustrated.

### Occlusion of the Hepatic Veins

*J. B. Gibson* (1958)

In five cases of Chiari's disease the hepatic veins were occluded at the ostia, apparently before the onset of symptoms. Congestion of the liver and focal necroses resulted. Massive ascites developed from transudation of liver lymph. Similar clinical results can follow occlusion deeper in the veins (Budd-Chiari syndrome).

### Obstruction of the Portal Vein

*H. W. Rodgers* and *J. B. Gibson* (1958)

Data were presented from cases observed in Belfast in relation to clinical manifestations, radiological and other diagnostic features, operative findings, and prognosis.

Pathological material was demonstrated from eight cases occurring in Glasgow and Belfast of cavernous transformation of the portal vein.

#### Reference

Gibson, J. B., and Richards, R. L. (1955). *J. Path. Bact.*, **70**, 81.

### Serum Protein Electrophoresis Patterns in Liver Disease

*D. W. Neill*

The use of apparatus for the automatic scanning and recording of paper electrophoresis strips was demonstrated and typical records were shown.

*Gut*, 1960, **1**, 87.

# CROHN'S DISEASE (REGIONAL ENTERITIS) OF THE LARGE INTESTINE AND ITS DISTINCTION FROM ULCERATIVE COLITIS

BY

H. E. LOCKHART-MUMMERY and B. C. MORSON

*From the Research Department, St. Mark's Hospital, London*

Twenty-five cases of Crohn's disease (regional enteritis) of the large intestine are described and illustrated. The clinical and pathological criteria for this diagnosis are discussed with emphasis on the distinction from ulcerative colitis. Suggestions are made regarding the surgical treatment of these patients.

The pathogenesis of many of the inflammatory diseases of the large intestine is imperfectly understood and the literature contains many conflicting views, and so no classification has been generally accepted. Apart from specific diseases such as diverticulitis, bacillary dysentery, amoebic dysentery, and lymphogranuloma venereum, there remains to be considered a group of conditions which have been given an abundant and confusing nomenclature. These include such expressions as "regional colitis", "right-sided colitis", "segmental colitis", "enterocolitis", "ileocolitis", "ulcerative colitis", and "regional enteritis", all of which are largely the result of attempts at classification based on clinical research. Some authorities, notably Goldgraber and Kirsner (1958); Goldgraber, Kirsner, and Palmer (1959) favour a unified approach to these conditions based on aetiological theories of hypersensitivity or auto-immune disease. Others have attempted to classify them more accurately by study of the gross and microscopic appearances in surgical material, correlating the clinical and pathological appearances, and, as a result, the conditions we call "chronic ulcerative colitis" and "regional enteritis or Crohn's disease" have become more definite clinical-pathological entities in recent years. Apart from staphylococcal enterocolitis the other expressions referred to above, such as "segmental colitis" and "ileocolitis", are valueless from the point of view of classification based on pathogenesis. Moreover, they have added to the general confusion because different authors use them to refer to differing pathological conditions.

In this article we describe a clinico-pathological study of 25 patients with localized or diffuse inflammation of the large intestine whom we believe to have the same disease as that described by Crohn, Ginzburg, and Oppenheimer in 1932. In order to avoid further confusion we have preferred to use the eponymous term "Crohn's disease of the large intestine", because our patients had the same characteristic pathology in the large intestinal lesions as that described by Hadfield (1939) for the disease as it affects the small intestine. The fact that Crohn's disease could affect the colon was first mentioned by Colp in 1934 and noted by Crohn and Rosenak in 1936. Since that time there has been much confusion over the relationship between Crohn's disease and ulcerative colitis. This expression "Crohn's disease of the colon" was first used by Wells (1952) and later by Brooke (1959). It is not our purpose to go into the aetiological factors which may be common to these two diseases, but only to emphasize that Crohn's disease of the large intestine and chronic ulcerative colitis can be distinguished on clinical and pathological evidence and that this may have therapeutic implications.

The 25 patients with Crohn's disease of the large intestine presented here were treated at St. Mark's Hospital during the five-year period 1955-1959, and in all of them operation specimens have been available for pathological examination. Our experience with the pathology of this condition has been augmented, however, by the examination of a further nine operation specimens of Crohn's disease affecting the large bowel from patients who received surgical treatment at other hospitals during the same period. Cases of recurrent Crohn's disease at or distal to the ileocolic anastomosis after surgical resection for disease of the small intestine have been excluded from this study. During the same five-year period, 156 patients with chronic ulcerative colitis

were treated surgically at St. Mark's Hospital; 20 cases of Crohn's disease affecting the small intestine only have also been seen, as well as four cases of "regional colitis" in which there were no pathological features to suggest Crohn's disease. When considering these figures, it must be remembered that St. Mark's is a special hospital for diseases of the colon and rectum to which patients with disorders of the large bowel are likely to be referred, so a particularly high proportion of involvement of the large bowel among the cases of Crohn's disease seen there is not as surprising as it would appear, nor do we suggest that our figures are representative of the distribution of Crohn's disease generally. We recognize now that cases of this condition have been seen at this hospital more than five years ago, but at that time they were not recognized as being cases of Crohn's disease of the colon, and in many of them neither the pathological material available nor the clinical notes were as full and adequate as are available nowadays. We have, therefore, excluded these cases from this presentation.

## Classification and Case Reports

In a previous paper (Morson and Lockhart-Mummery, 1959a) we classified some of these 25 cases into two main groups, namely, (1) diffuse disease of the colon and (2) strictures of the colon. This classification was based on the location of the intestinal lesions in operation specimens. Further experience has confirmed that this is a useful subdivision, but in this paper we are also presenting as a separate group some patients in whom the disease has predominantly affected the rectum. We have therefore classified them as follows:

(1) Diffuse Disease of Large Intestine.—Most or the whole of the large bowel was diseased, in the majority of cases, with patches of normal mucosa. This group of 13 cases was further subdivided according to the presence or absence of similar disease in the terminal ileum.

(2) Localized Disease.—Patients with only a short segment of the colon affected or more often with multiple strictures and extensive areas of normal intervening mucosa: there were six patients in this group.

(3) Disease Mainly Confined to Rectum.—There were six patients in this group.

Diffuse Disease of Large Intestine.—Of the 13 patients in this group there were nine men and four women. Six, all of whom were men, had involvement of the terminal ileum. Cases 4 and 7 were brothers, aged 22 and 27, but only one of them had disease of the terminal ileum. The average age of this group of cases was 27 years at the time of treatment, the youngest being 17 and the oldest 49, 10 of them being under 30. The duration of their symptoms from onset to the time of treatment varied from six months to 12 years, but in the majority it was between one and two years. The youngest patient was 15½ years at the time of onset of symptoms and the oldest was 47 years old.

The extent of the disease in these patients is shown in Figs. 1 and 2, Fig. 1 showing those cases with involvement of the ileum as well as the colon, and Fig. 2 those in which the terminal ileum and the rest of the small bowel were quite normal. It will be seen from Fig. 1 that Case 1 is the only patient in whom the whole of the large bowel was involved as well as the small bowel, and as he presented many features which we now believe to be typical of this condition, we present his history in some detail.

*Case* 1.—This young man was 19 years old when first seen in 1948. He was referred because of an anal fistula and gave a history of anal disease with some diarrhoea for six months. At this first examination sigmoidoscopy was normal but he had a complex anal fistula, clinically tuberculous, and was admitted for operation. The fistula was operated on a few weeks later and giant cell systems were found in biopsy material. A diagnosis of tuberculous fistula-in-ano was made at that time, but the patient did well and the fistula healed within three months. A chest radiograph was normal. He was seen annually between the years 1949 and 1954 and remained well except that he had mild diarrhoea with his bowels acting two to three times a day, passing a semi-formed motion. In 1954 he suddenly became very much worse, with intense diarrhoea, pyrexia, loss of weight, and some blood in the motions. At this time, sigmoidoscopy showed a granular rectum and it was noted that the anal fistula had recurred. Barium enema examination showed a generalized contraction and polypoid appearance of the large bowel. A search was made for tubercle bacilli, both by staining and culture methods and by guinea-pig inoculation, but proved negative. The patient was regarded as a case of severe ulcerative colitis, and as there was no response to medical treatment a laparotomy was done with a view to colectomy. At operation the ileum as well as the colon was found to be diseased, and several inches of the terminae ileum were therefore removed with the whole of the colon and an ileostomy established. Three months later the remaining recto-colic segment was excised. The patient made a good immediate recovery but the perineal wound took several months to heal. However, at the time of writing, five years after his operation, he is very well, working full time and with a normally functioning ileostomy.

The operation specimen is shown in Fig. 3. There is disease of the terminal ileum with extensive involvement of the colon and the appearances are similar to those

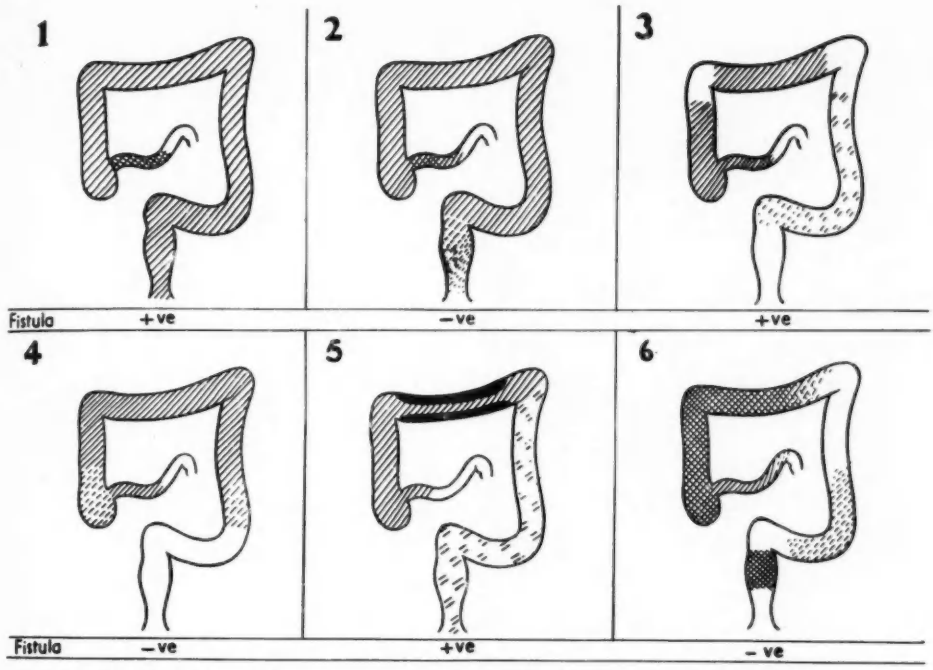


FIG. 1.—*Cases 1-6. Diffuse disease of the large intestine with involvement of the terminal ileum.*

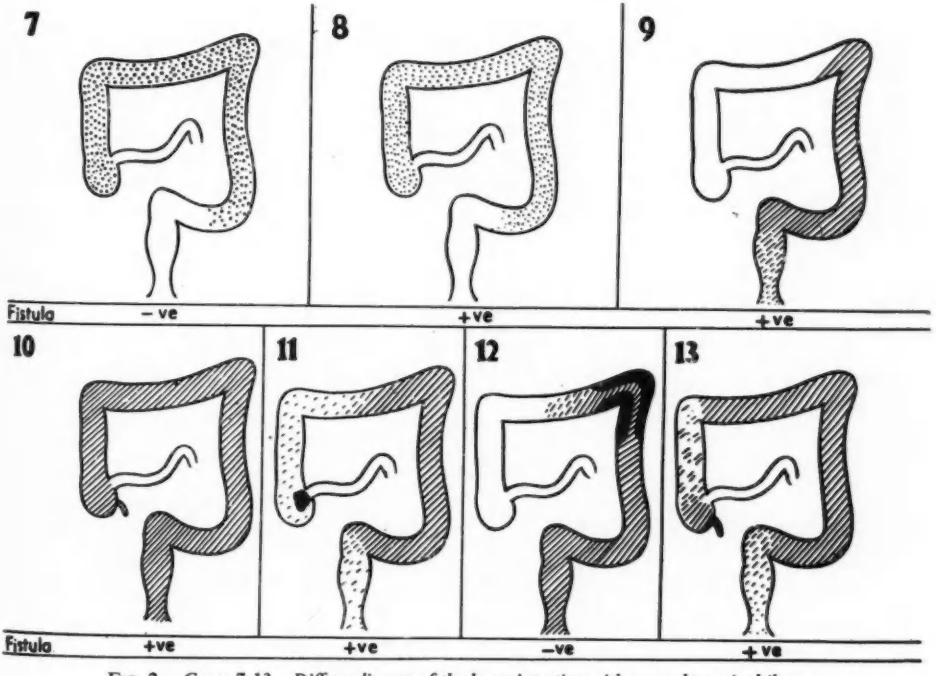


FIG. 2.—*Cases 7-13. Diffuse disease of the large intestine with normal terminal ileum.*

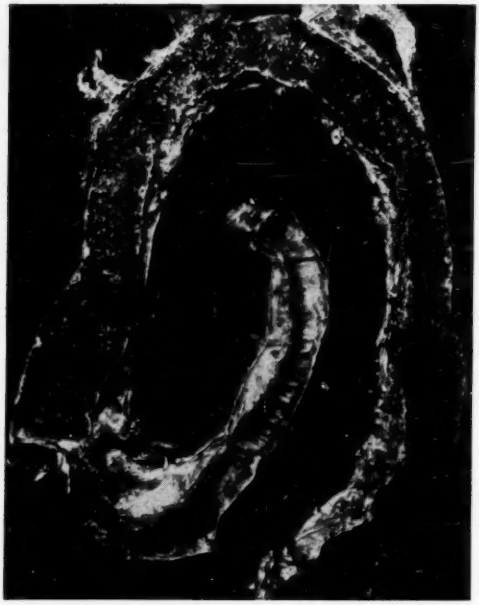

FIG. 3.—*Operation specimen from Case 1. There is a contracted terminal ileum with mucosal ulceration especially in the distal six inches and thickening of the bowel wall. The ileo-caecal lymphatic glands are grossly enlarged. The appearances of the colon are similar to those seen in ulcerative colitis with inflammatory polyposis.*

seen in ulcerative colitis. However, the histology of both the terminal ileum and of sections taken from different parts of the colon showed appearances characteristic of Crohn's disease.

It is not surprising that five of these 13 patients had been regarded as cases of ulcerative colitis at some time during their illness, and that a further three patients had been regarded as suffering from tuberculous colitis, largely because of the clinical appearance of the anal lesions. Case 10, a patient who had extensive anal ulceration, was treated originally at this hospital by a sigmoid colostomy, but developed undermining ulceration around the stoma, which seemed to confirm the tentative diagnosis of tuberculosis.

LOCALIZED DISEASE.—Of the six patients in this group there were four men and two women. The terminal ileum was diseased in one of the male patients only.

The average age of this group was 54 years, the youngest patient being 34 at the time of treatment and the eldest 72. The duration of symptoms varied from one year to seven years before surgery was undertaken, but in three of the six symptoms had been present for one year only, although one of these three had had two anal fistulae 18 years and 12 years before the onset of diarrhoea.

The extent and distribution of the disease in these six patients is shown in Fig. 4. It will be seen that the disease is patchy in its distribution, short segments of diseased bowel being separated by relatively long segments of normal intestine. In all six patients the areas of disease had led to narrowing of the lumen which in a few of them was sufficiently severe to be called a definite stenosis. Obvious ulceration in the diseased areas was only seen in two of the six operation specimens, the others showing thickened muscle, fibrosis, and stenosis. The gross appearance gives the impression of a more inactive, "burnt-out" disease than in the operation specimens of the diffuse group. This observation is in keeping with the older average age of these patients, but the duration of symptoms is much the same in the two groups; it is possible that in these patients the symptoms resulted from the stenosis rather than from active disease. Case 14 is a good example of this group of patients.

*Case* 14.—This man was first seen at St. Mark's Hospital in 1955 at the age of 69. He had diarrhoea in 1951 with an ulcer in the rectum. In 1953 he had a laparotomy for a large bowl lesion but no resection or anastomosis. In 1955 he complained of increasingly severe diarrhoea with blood in the stools and some degree of incontinence. Examination of the rectum showed pus in the lumen and a curious granulomatous lesion in the middle rectum. A barium enema showed a filling defect in the transverse colon. Another laparotomy was done and the only abnormality in the abdomen was a localized lesion in the middle of the transverse colon which appeared to be inflammatory. The rest of the large bowel and all the small bowel appeared normal but the upper rectum felt somewhat thickened. A resection of the transverse colon with immediate end-to-end anastomosis was carried out. The patient did well after the operation but remained incontinent and the lesion in the rectum seemed to be getting rather worse. Accordingly, a left inguinal colostomy was established. From then on the patient made good progress and gained weight but the lesion in the rectum caused progressive stenosis and it has never been possible to close the colostomy. At the time of writing, four years after the operation, the patient is well and with a satisfactorily acting colostomy, but with considerable stenosis of the rectum.

The specimen of the lesion removed by resection of the transverse colon is shown in Fig. 5. It shows obvious narrowing of the lumen and thickening of the bowel wall over a distance of about 4 in. The histological appearances were those of Crohn's disease.

In one of these patients (Case 15) a diagnosis of

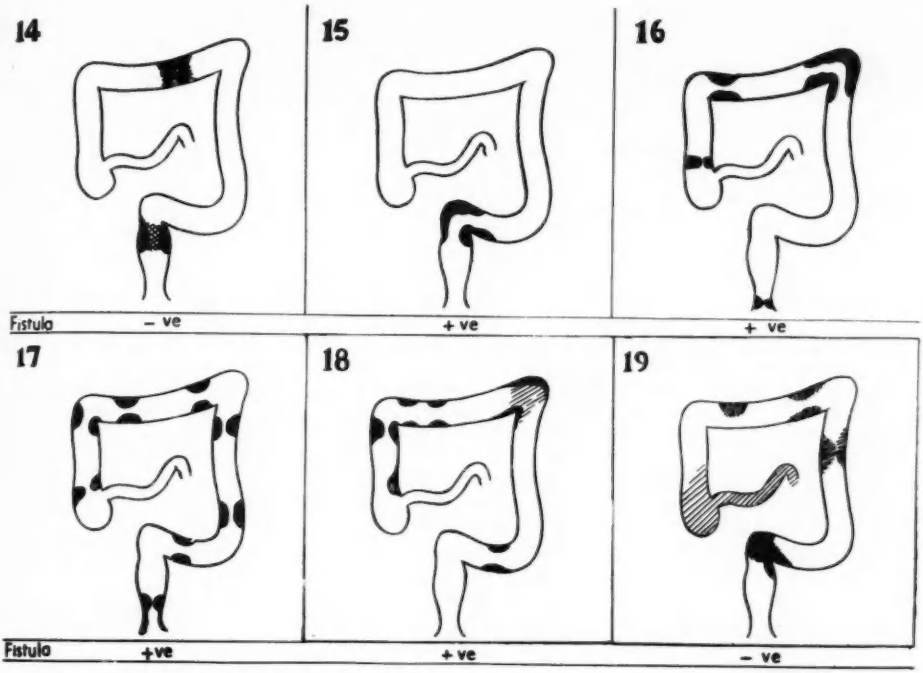


FIG. 4.—*Cases 14-19. Localized disease of the large intestine presenting in the form of multiple strictures. There is associated disease of the small intestine in only one case, No. 19.*

FIG. 5.—*Colectomy specimen from Case 14. The lumen is narrowed and the wall thickened over a segment of transverse colon about 4 in. long with extension of the granulomatous process into the pericolic fat.*

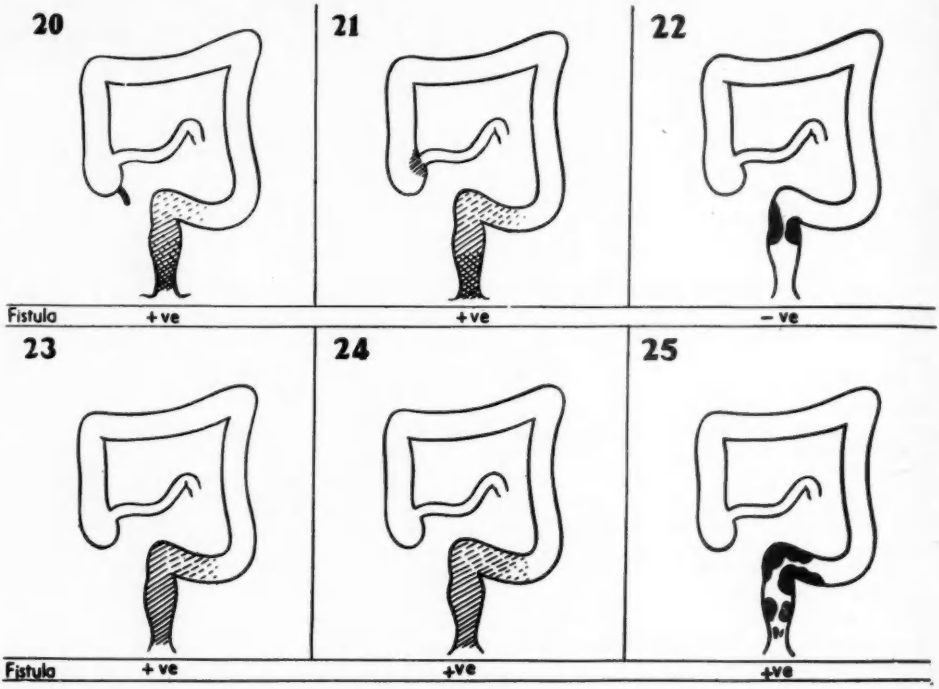


FIG. 6.—*Cases 20-25. Disease mainly involving the rectum and rectosigmoid region. Two cases also had disease of the appendix (Case 20) and ileo-caecal valve (Case 21).*

"tuberculous colitis" had been made previously, partly because of the presence of two sinuses in the left loin and partly because of an anal fistula with an indolent appearance. Case 16 had been diagnosed as "ulcerative colitis" during her first attack, five years before treatment at St. Mark's. In the other patients the diagnosis was uncertain in the early stages and was only made by pathological examination of a piece of resected colon.

DISEASE MAINLY INVOLVING THE RECTUM.—There were six patients, four men and two women, in whom the disease predominantly affected the rectum and rectosigmoid region. The average age was 43 years, the youngest being 15 and the oldest 56. The duration of symptoms varied from six to 12 months, but one patient had had symptoms for three years.

The extent and distribution of the disease in this group is shown in Fig. 6. It will be seen that two patients (Cases 23 and 24) had involvement of the rectum and lower sigmoid colon only. Two others had a similar distribution of disease but with isolated lesions of the appendix in one case and the ileocaecal valve in the other. One patient had a single localized stricture of the rectum. Case 20 is a good example of this group of patients.

*Case* 20.—This youth was first seen at St. Mark's Hospital in October, 1957, when he was 15 years old. He gave a history of diarrhoea for the previous six months, passing two to four loose, offensive stools daily. A trace of blood had been noticed on one occasion only. He had lost about a stone in weight, and had felt generally rather unwell. Examination showed him to be rather pale and sallow, but abdominal examination revealed no abnormality. The perianal region was oedematous, inflamed, and tender, with superficial tender cracks and a fistula discharging pus. There was some stenosis at the level of the anorectal ring and examination caused pain. Sigmoidoscopy under anaesthesia showed patchy areas of oedematous granular mucosa and scattered ulcers in the rectum, with pale normal mucosa between the affected parts. There was much free pus in the lumen. A chest radiograph and a barium enema were both normal.

Biopsy from the anal fistula showed giant-cell systems, but no tubercle bacilli could be demonstrated. Never-

theless, he was thought to have a tuberculous infection, and was transferred to a sanatorium near his home. In spite of general measures and treatment with streptomycin, I.N.A.H. and prednisone, however, the anorectal condition increased in severity and several perianal abscesses formed which required drainage. A left inguinal colostomy was established in March, 1958, but led to only slight improvement. At this time repeated culture of the pus from the rectum and guinea-pig inoculation were negative. Laparotomy was carried out in October, 1958, but all viscera were found to be normal apart from the lower sigmoid colon and rectum which were thickened; a biopsy from the perirectal tissue was taken. Sections again showed non-caseating giant-cell systems, and a diagnosis of Crohn's disease appeared to be most likely.

He was readmitted to St. Mark's in January, 1959, having by then developed considerable anal stenosis with several undermined painful anal ulcers. The disease appeared to be confined to the rectum and anus, and there seemed to be no useful alternative to excision of this part of the bowel. This was done by combined excision, the sigmoid colon being removed up to the colostomy, which was converted to a terminal one. All other viscera appeared normal, except that the spleen was somewhat enlarged, but the appendix was removed. Recovery was delayed by an attack of intestinal obstruction, but was thereafter uneventful, and now a year later he is in excellent health, without symptoms, and working full time.

The specimen (Figs. 7 and 8) showed oedema and scattered ulceration of the whole rectal mucosa, with a large ulcer in the lower third. There was considerable fibrous thickening of the wall in the lower part of the rectum, and many anal fistulae were found. Histology both in the bowel wall and in the lymph nodes was typical of Crohn's disease, and similar changes, including giant-cell systems, were found in the appendix.

Three of these six patients were at first regarded as cases of procto-colitis. This diagnosis was later changed to "tuberculous colitis" in two of them when fistulae developed in which giant-cell systems were found, and two other patients had been diagnosed as cases of tuberculosis on the evidence of anal lesions. In Case 22 the hard and localized nature of the lesion led to a clinical diagnosis of rectal carcinoma, and although biopsy was negative, excision of the rectum was advised and carried out in the belief that the lesion was due to the submucous spread of a rectal cancer. A study of Figs. 1, 2, 4, and 6 will show that the grouping of these cases is not exact. For instance, Case 22 may have more in common with the patients in Group 2 than with those in Group 3, and Case 19 in Group 2 is very similar to those in Group 1. We emphasize, however, that we are not attempting to set forth an accurate classification but only to present a series of cases in a coherent and intelligible way. It may be that further experience and study of a larger series of cases over the next years will suggest a classification which will be more exact and acceptable.

### Summary of Clinical and Radiological Findings

History.—Diarrhoea is by far the most common symptom and was present at some time in all our cases, and in the majority was at all times the main complaint. According to the extent and severity of the disease, it varied from mild to severe and was in most cases continuous, but was in some recurrent with periods of remission. In those cases with strictures of the colon, attacks of diarrhoea were usually accompanied by some abdominal colic, although abdominal pain was not the main complaint in any patient; while in those patients with disease affecting mainly the rectum, morning diarrhoea and urgency were frequent features. Passage of blood in the stool was not common and was usually only mentioned as a symptom by those with disease involving the rectum. Loss of weight was a feature of many cases and a general malaise and lethargy were frequently revealed on questioning. In those patients admitted with an acute relapse, pyrexia was common.

Anal Lesions.—A very high proportion of these patients, 17 out of the 25, had at some time during the course of their illness a lesion of the anus or perianal region (see Figs. 1, 2, 4, and 6). As might be expected, they were particularly common in those patients with disease involving the rectum, though not confined to such patients. A few of the patients gave a history of having had an anal fistula in the past, but in a larger number an anal lesion was present when the patient was first seen at the hospital. The commonest lesion was an anal fistula which was often, but not always, indolent and lacking in induration, but curious undermining anal ulceration were seen in a few patients, and others had anal fissures that appeared indolent and infected. Often there was oedema of the skin of the perianal region and frequently the anal lesion was extremely painful.

In some patients the anal lesion had been the first sign of disease, and in Case 11 a large and painful ulcer at the anus remained throughout her illness the most distressing symptom, though diarrhoea and weight loss occurred later. In most other patients diarrhoea or other bowel symptoms preceded the onset of an anal lesion, in one case by 12 years; in some cases the anal lesion appeared about the same time as the bowel symptoms started.

The association of anal lesions with intestinal Crohn's disease is well known but we wish to draw

FIG. 7

FIG. 7.—*Case No. 20. Operation specimen of abdomino-perineal excision of lower sigmoid colon, rectum, and anal canal, showing ulceration and stenosis of the lower third of the rectum with a nodular condition of the mucosa of the upper rectum and sigmoid colon due to granulomas in the submucous layer.*

FIG. 8.—*Close-up of Figure 7.*

FIG. 8

attention to the particularly high incidence of this complication in cases of Crohn's disease in which the large bowel is affected (Morson and Lockhart-Mummery, 1959a and b).

SIGMOIDOSCOPY.—As can be seen from Figs. 1, 2, 4, and 6, in many of these 25 patients the disease did not extend to the rectum, and in most such patients the rectum was perfectly normal on sigmoidoscopy, although in a few of them slight oedema was noticeable. In most patients in Group 2, the lowest stricture could either be felt with a finger or reached with the sigmoidoscope; the mucosa was usually normal as far as the lower border of the stricture, at which level the bowel could be seen to be reddened, narrow, and rigid. Actual ulceration at the stricture could sometimes be seen, and where an active ulcerative lesion was present pus was seen in the lumen of the bowel.

In those patients of Groups 1 and 3 in whom the bowel was extensively involved, definite abnormalities of the rectal mucosa were found on sigmoidoscopy. In some of them the appearance was that of a uniformly granular bowel, bleeding on touch, and apparently indistinguishable from that caused by ulcerative colitis. In others, however, a different picture was seen; the mucosa was reddened and oedematous but not granular, and small scattered ulcers could be found (see Fig. 8). These ulcers varied in depth but often appeared infected with a little surrounding congestion, and the base was sometimes obscured by purulent discharge. In a few patients areas of granular bowel or of groups of ulcers were separated by areas of normal or slightly oedematous mucosa.

RADIOLOGICAL APPEARANCES.—Most of this series of patients had had a barium enema examination carried out at some time, and many of them had also had a barium meal and follow-through. The radiological appearances naturally depend on the distribution and severity of the disease. As already mentioned, ulcerative colitis is a disease that nearly always extends in continuity, and the appearance of scattered areas of disease separated by normal parts is very suggestive of Crohn's disease, as is also the appearance of localized strictures of the bowel (Fig. 9). Disease that is more severe on the right side of the colon than on the left is more likely to be Crohn's disease than ulcerative colitis (Fig. 10).

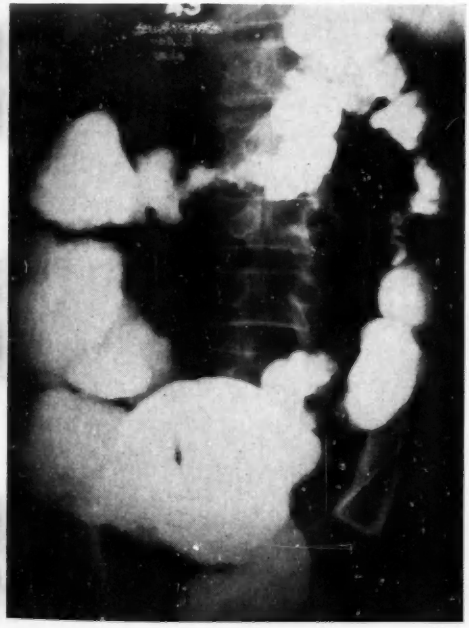

FIG. 9.—*Case No. 17. Multiple localized strictures of the colon.*

FIG. 10.—*Case No. 6. Diffuse disease of the colon mainly confined to the right half.*

FIG. 11.—*Case No. 19. Multiple strictures of the transverse colon with intervening normal mucosa.*

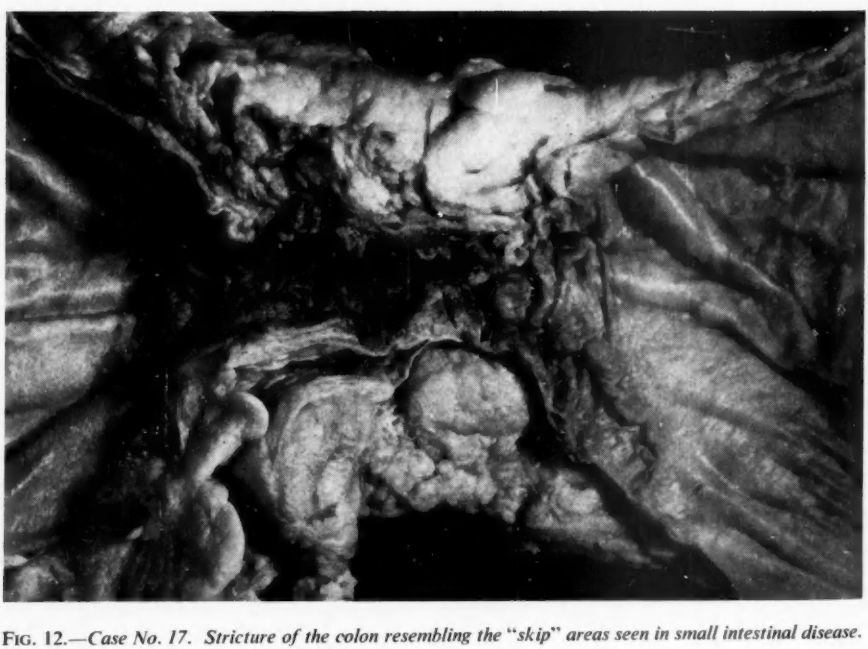

FIG. 12.—*Case No. 17. Stricture of the colon resembling the "skip" areas seen in small intestinal disease.*

Reflux of a barium enema through the ileo-caecal valve which demonstrates narrowing of the terminal ileum as well as an abnormal colon suggests Crohn's disease, as the terminal ileum which becomes involved in the retrograde spread of ulcerative colitis is characteristically dilated. The clinical features of these cases do not differ greatly from group to group; diarrhoea, pain, bleeding, and loss of weight are symptoms common to most disorders of the large bowel. As sometimes occurs in cases of ulcerative colitis, the onset of severe symptoms followed an anal operation in three patients, for haemorrhoids in two and for excision of a fissure in one. We have pointed out that in many of these cases a diagnosis of ulcerative colitis or tuberculosis was made at some time during the illness, and often the correct diagnosis was not apparent until the bowel had been removed and the histology studied. However, with increasing experience, cases presented at this hospital in recent years have in several instances been correctly diagnosed before operation, and we believe that in many cases the diagnosis can be established on clinical and radiological grounds, aided when possible by biopsy.

## Pathology

Appearances at Operation.—On opening the abdomen in a patient with Crohn's disease of the colon, the bowel usually appears obviously diseased. The external vascularity may be somewhat increased, and the peritoneal surface of the bowel may show signs of localized chronic inflammation with fibrosis and adhesions extending into the pericolic fat. A soft enlargement of the pericolic and ileocaecal lymph nodes is rather characteristic. The bowel feels thickened and rigid, and tiny "tubercles" may be seen on the peritoneal surface. In several of these cases it has been noted at operation that the spleen has been enlarged to two or three times its normal size.

Gross Appearances of Specimens.—In cases of Crohn's disease of the colon with diffuse disease of most or the whole of the large intestine, the appearances at first sight may resemble a case of ulcerative colitis, but careful examination reveals characteristics that are peculiar to Crohn's disease. In the first place, the ulceration is usually more sharply demarcated, and in all but one case there have been areas of intact intervening mucosa. This intervening mucosa may be lifted up to give the mammillated or nodular appearance which is seen so often in disease of the terminal ileum. In between these nodules small intercommunicating fissures may be found which penetrate deeply into the bowel wall and are the pathological basis of the intra-abdominal fistulae which often complicate intestinal Crohn's disease. In one of our colectomy specimens (Case 1, Fig. 3) the mucosal ulceration was very extensive and the surviving mucosa was markedly raised up to give the appearance of inflammatory polyposis. However, inflammatory polyposis is not a common feature of Crohn's disease of the colon as it is in ulcerative colitis.

In the operation specimens with single or multiple strictures the disease is well defined, involving a short segment of the bowel wall with fibrous thickening and narrowing of the lumen, and often ulceration (Fig. 11, Case 19). The adjacent mucous membrane is either normal or very slightly granular; the granular appearance can often be attributed to secondary infection from stasis of intestinal contents between areas of strictured bowel. The degree of thickening of the bowel wall in these cases varies with the chronicity of the disease. In specimens from patients with long-standing or "burnt-out" disease there may be very marked fibrous thickening with appearances similar to those seen in the "hose pipe" variety of classical Crohn's disease of the terminal ileum. The strictures in the colon closely resemble the "skip" areas so characteristic of small intestinal disease (Fig. 12, Case 17).

Fibrosis and oedema may be very pronounced in Crohn's disease and often extend into the pericolic fat (Fig. 13, Case 16). Enlargement of the regional nodes is marked and this is frequently a useful sign in the differential diagnosis from ulcerative colitis, in which enlargement of the nodes is not so striking.

The terminal ileum has been involved in seven of these 25 cases of Crohn's disease of the colon. The appearances of the terminal ileum in Crohn's disease have been fully described and there is no need to repeat them in detail here. The characteristic features are narrowing of the affected intestine with fibrous thickening of its walls and a nodular or mammillated appearance of the mucosa and some obvious mucosal ulceration. The ileocaecal valve is usually thickened but is visible as an obvious narrowing between small intestine and colon (Fig. 14, Case 6). In one specimen with disease of the distal sigmoid and rectum only, there was inflammatory ulceration and stenosis of the ileo-caecal valve but a normal terminal ileum (Case 21). In another with disease confined to the rectum there was isolated disease of the appendix (Case 20) which showed the histological appearance of Crohn's disease on microscopic examination. The appendix has been diseased in a number of other cases.

Microscopic Appearances.—Sections show that even in diseased areas the mucosal ulceration of the

FIG. 13.—*Case 16. Fibrous stricture of the splenic flexure with extension of the granulomatous process into the pericolic fat.*

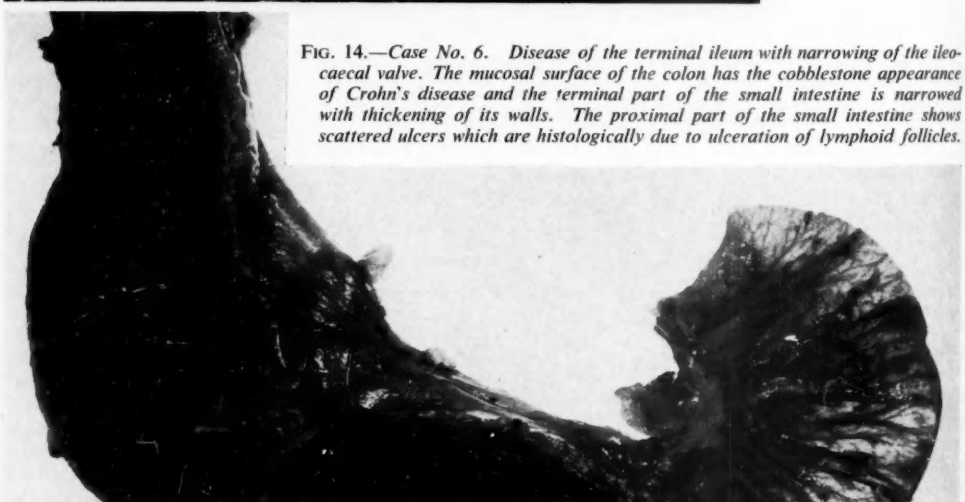

FIG. 14.—*Case No. 6. Disease of the terminal ileum with narrowing of the ileocaecal valve. The mucosal surface of the colon has the cobblestone appearance of Crohn's disease and the terminal part of the small intestine is narrowed with thickening of its walls. The proximal part of the small intestine shows scattered ulcers which are histologically due to ulceration of lymphoid follicles.*

colon in Crohn's disease is patchy, the intervening mucosa being normal or nearly so. The ulceration extends into and along the submucosa and at a later stage through the muscularis externa into the serosa and pericolic fat. This deep ulceration or fissure formation, which can be seen with the naked eye as well as with the microscope, is the basis of the fistula formation which is characteristic of Crohn's disease.

Surrounding these fissures as they penetrate the bowel wall is a chronic granulomatous reaction with oedema, hyperplasia of lymphoid tissue, and fibrosis. This chronic granulomatous reaction is particularly prominent in the submucosa where it lifts up the mucous membrane between the areas of ulceration to give the nodular or mammillated appearance which is found in many cases of Crohn's disease, whether of the small or large intestine. In most of the cases of Crohn's disease of the colon the granulomatous reaction includes non-caseating giant-cell systems which are distributed through all layers of the bowel wall, as well as in the regional lymph nodes (Figs. 15 and 16). These giant-cell systems consist of one or more rather small multinucleated giant cells lying in a network of epithelioid cells mixed with mononuclear cells, principally lymphocytes. They are smaller than those in tuberculosis and never show central caseation, though a little central necrosis is occasionally seen. The giant-cell systems of Crohn's disease resemble sarcoid and may be justifiably referred to as a sarcoid reaction. But for the fact that patients with Crohn's disease never develop generalized sarcoidosis, it would be tempting to regard Crohn's disease and sarcoid as having a common aetiology. Moreover, in a few of our cases of Crohn's disease occasional giant cells have contained Schaumann and hyaline inclusion bodies identical with those seen in sarcoidosis (Fig. 17).

The discovery of giant-cell systems in these cases of Crohn's disease of the colon has been an important diagnostic feature, and they have been present in the majority of our cases. However, the distribution of the lymphoid hyperplasia, oedema, and fibrosis, together with the appearance of the mucosal ulceration and the formation of deep fissures in the bowel wall, make up a histological picture which can be diagnostic of Crohn's disease even in the absence of giant-cell systems. It is important to investigate many lymph nodes, taken from both the ileo-caecal and pericolic groups, for such systems. Their presence is not always related to the size of the glands and often very small nodes may be affected. The number of giant-cell systems in the bowel wall varies greatly and it is necessary in the investigation of a case of Crohn's disease of the colon to take pieces of tissue for section from several parts of the large intestine.

There is considerable evidence that Crohn's disease is a disease of lymphoid tissue. Certainly it is most common in the terminal ileum which has the largest aggregation of lymphoid tissue in the gastro-intestinal tract. Histologically, the appearances suggest that the disease starts in the lymphoid follicles of the intestine with ulceration of the overlying mucosa and extension into the submucous tissue. In one of our cases the normal lymphoid follicle in a non-ulcerated part of the colon showed hypertrophy and contained giant-cell and epithelioid-cell systems (Fig. 18). In another case the earliest changes were apparently the result of ulceration of the lymphoid follicles and Peyer's patches in the terminal ileum. The granulomatous reaction is commonly related to the course of the blood vessels within the intestinal wall. It is possible that these granulomas occur within and around lymphatic vessels which are blocked and this is the cause of the marked oedema of the bowel wall and mesenteric tissues seen in active Crohn's disease.

## Treatment

All 25 patients in this series have been treated surgically, but we do not suggest that they represent a fair sample of the disease generally. For one thing, as we have explained previously, these patients were selected in that only those in whom the diagnosis was regarded as certain and in whom good pathological material was available were included; moreover, patients are often referred to this hospital especially for surgical treatment. Many of these patients have at some time or other been treated medically, and good remission of the disease has occurred, either spontaneously or as a result of the medical treatment. It is likely that in many patients with Crohn's disease of the colon satisfactory remission and control of the disease for long periods can be obtained by medical treatment. Nevertheless, the patients in this series have either become severely ill or have developed complications such as strictures or fistulae and had not responded, or were no longer responding, to medical treatment.

Several different procedures have been employed in the treatment of these patients, and many patients have had more than one operation, sometimes as part of a deliberately staged procedure, sometimes because the first operation was not successful. Where possible, intestinal continuity has been restored, but in many cases an ileostomy or colostomy has been considered necessary for cure. So of these 25 patients, nine have had a total proctocolectomy and now have a permanent ileostomy;

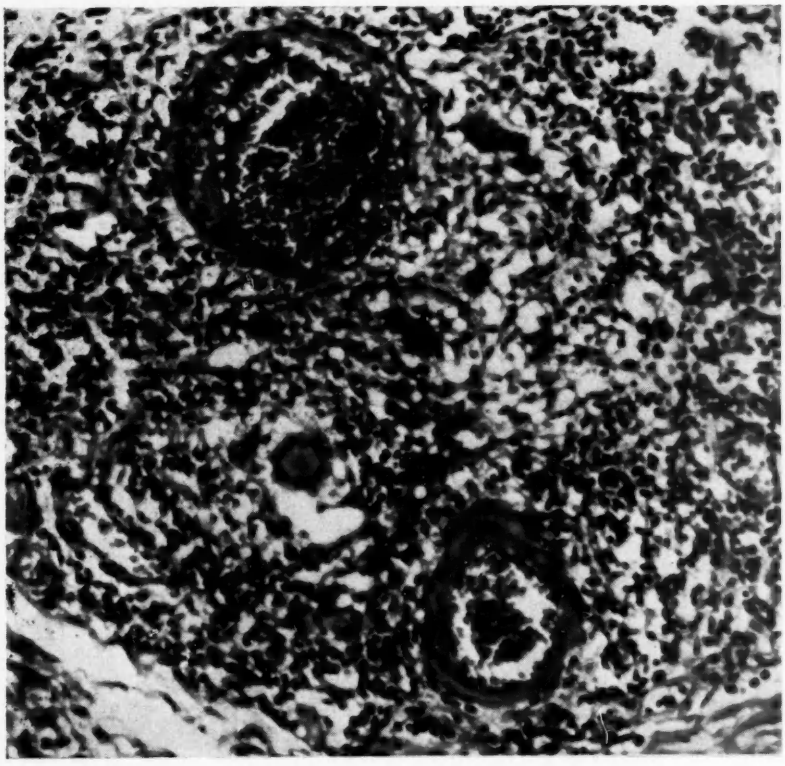

FIG. 15.—*Granulomatou reaction in Crohn' disease showing the non caseating giant cell syste closely related to th course of blood vessels.*

FIG. 16. — *Non-caseatin giant cell and epithelioi cell systems in a lym phatic gland. The ap pearances resemble sa coid.*

FIG. 17.—*Crohn's disease o the colon. Schaumann and hyaline inclusion bodies within giant cel similar to those seen i sarcoidosis.*

FIG. 18. — *Collection o epithelioid cells and smal giant cells in a lymphoi follicle of the colon fro a case of large intestina Crohn's disease.*

FIG. 15

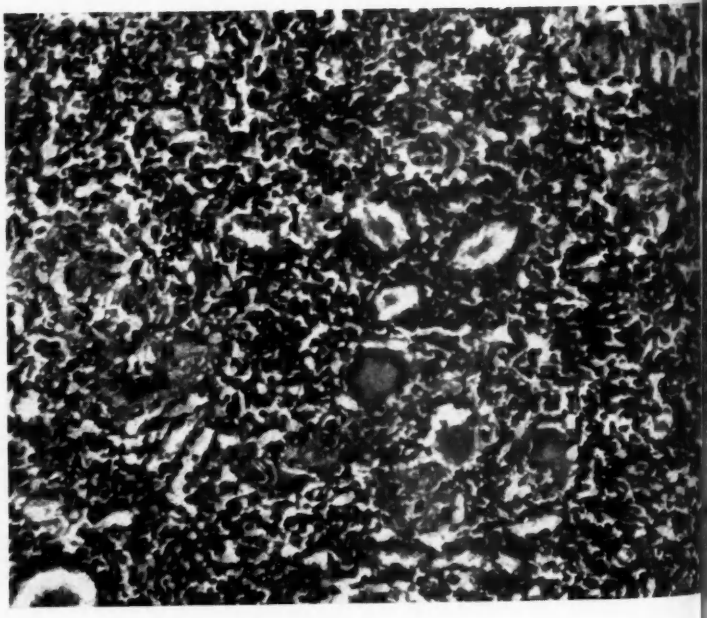

FIG. 16

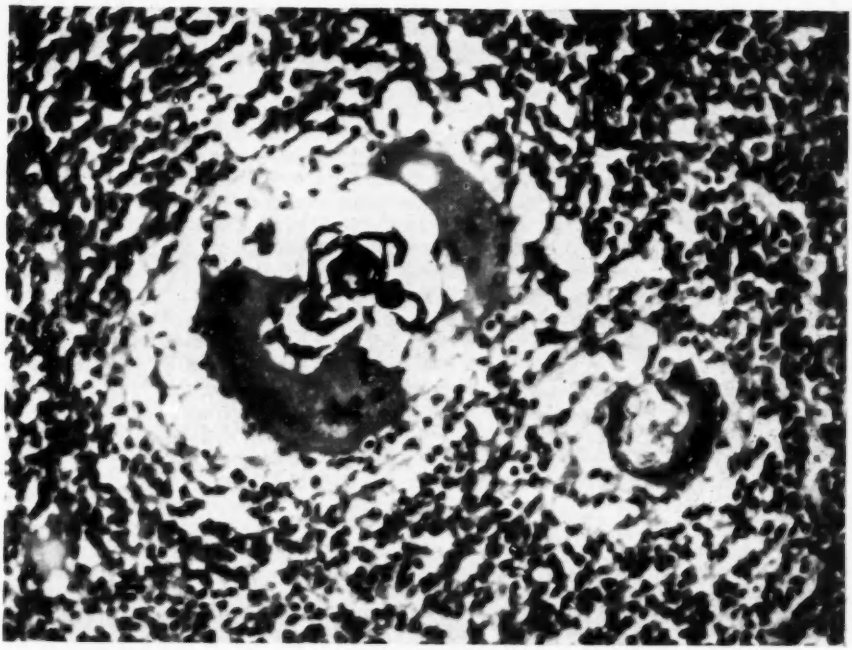

FIG. 17

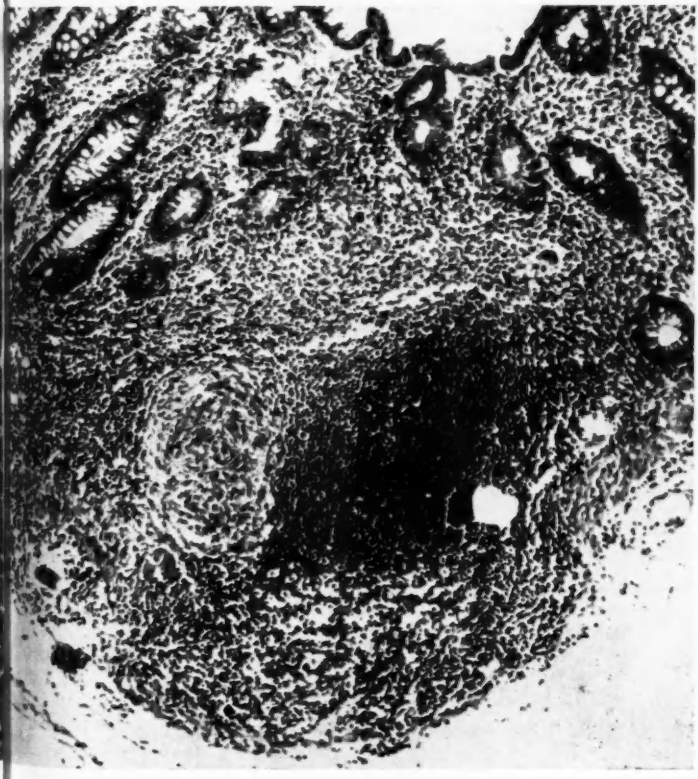

FIG. 18

seven have had a colectomy with preservation of the rectum and ileo-rectal anastomosis; five have had an excision of the rectum with permanent inguinal colostomy; two have had a partial resection of the colon with anastomosis; and two have had an ileostomy with subtotal colectomy and await a further stage, possibly ileo-rectal anastomosis, perhaps excision of the rectum. There has been one death in these patients following surgery, a woman (Case 25) who died of shock and haemorrhage following an excision of the rectum and hysterectomy.

Complications following surgery have been those that one might expect in any series of major abdominal operations, except that indolence and slow healing of the perineal wound has been observed in four of the patients from whom the rectum was removed (13 operation survivors). We regard this as significant, as healing of the perineal wound is usually complete at this hospital in six to eight weeks after excision of the rectum, while in these patients it took six months or longer. Biopsies were taken from these indolent perineal wounds and in one of them giant-cell systems, similar to those previously found in the bowel, were found. Nevertheless, sound healing finally took place in these four patients.

We have kept in touch with all these patients after surgery to see how they have progressed, and most of them attend at regular intervals as outpatients. It appears that the results after excision of the affected bowel have been good, whereas those following faecal diversion without removal of the diseased bowel have usually been bad. Thus, all patients who have had a total colectomy and ileostomy are well, the elapsed time since operation varying from one to five years. Five of the patients treated by ileo-rectal anastomosis are perfectly well, but in two there is some residual proctitis; one has had a recurrence of an old anal fistula. However, no further surgery for these two patients is contemplated at the moment as they are in good health. The four patients who had an excision of the rectum only are well, two for five years, one for three years, and one was only treated one year ago. One of the patients treated by a localized resection of the colon had to have a further operation later because of disease in the rectum (Case 14) but the other has remained well.

On the other hand, seven patients had at some time a diversion operation with the hope of inducing remission of active disease. Five had had a colostomy (Cases 12, 20, 21, 23, and 24) and two an ileostomy (Cases 10 and 25). Only one of these patients did well after diversion alone; this young man (Case 10) fully regained his health and put on a lot of weight after ileostomy, though continued activity and discharge from the defunctioned but diseased bowel was considered sufficient reason, a few years later, for its removal. The other six patients were not benefited by diversion of faeces. Active disease in the bowel persisted in spite of continued medical treatment, their health did not improve, and they were only restored to health by excision of the diseased bowel, since when they have remained well. However, we should say here that we know of two further patients at this hospital with Crohn's disease of the colon in whom an ileostomy was done, in both of whom dramatic improvement took place, though colectomy may later become necessary. (They are not included in the series because no specimen was available for pathological study.)

From a study of these cases and from others seen at the hospital, we get the impression that in Crohn's disease affecting the large bowel medical measures have not been very successful and that surgery seems to offer a better prospect of a return to normal health and of prolonged freedom from disease. As in most clinics, the practice at St. Mark's Hospital in cases of ulcerative colitis in which medical treatment has failed has been to excise the colon: usually ileostomy and total proctocolectomy in one or two stages is done, with preservation of the rectum and ileo-rectal anastomosis in certain selected cases. In Crohn's disease of the large intestine, however, we consider that localized resection of the diseased part of the bowel with anastomosis is desirable where possible; if this is not possible, we think that a diversion operation only (ileostomy or colostomy) may have a place and should be tried in the first instance.

With such a small series of cases and with a longest follow-up of only five years, it would be unwise to be dogmatic. Nevertheless, the results of excisional surgery have been encouraging so far. We hope that experience may show that Crohn's disease of the colon has a lesser tendency to recur after excisional surgery than does Crohn's disease affecting the small bowel.

## Discussion

There is much confusion over the relationship between Crohn's disease and ulcerative colitis. The literature contains reports of Crohn's disease of the terminal ileum with disease of the colon regarded by the authors as the simultaneous occurrence of two separate conditions, namely Crohn's disease and ulcerative colitis. It is recognized, however, that Crohn's disease may affect the colon, though this is thought to be rare. Yarnis (1958) presents 64 cases

of "ileo-colitis", and of these he regards 60 as being a combination of granulomatous ileitis and ulcerative colitis (which he calls "combined ileo-colitis") and only four as examples of granulomatous ileo-colitis. Daffner and Brown (1958) report a series of 100 cases of Crohn's disease and record that 37% of them had "ileo-colitis", but do not describe the pathology of these cases. French and Vander (1955) discuss ulcerative colitis and "regional entero-colitis", but do not make a clear distinction between the two conditions. Warren and Sommers (1954) consider that the simultaneous occurrence of Crohn's disease and ulcerative colitis is very rare, and a similar opinion is expressed by Otani (1955), writing from the Mount Sinai Hospital, who regards such an association as coincidental. There is, therefore, a good deal of controversy in the published literature as to the frequency of association of these two diseases and whether Crohn's disease may give rise to pathological changes in the colon similar to those found in the terminal ileum.

We have never seen Crohn's disease and ulcerative colitis in the same patient, and believe that when Crohn's disease of the terminal ileum coexists with ulceration in the colon, histological examination will reveal that the colonic lesions have the same pathology as the Crohn's disease in the small intestine. Moreover, it does not seem to be fully appreciated that Crohn's disease may affect the large bowel without any disease in the small intestine, and may even be confined to the rectum and distal sigmoid colon.

Crohn's disease of the colon may be differentiated from ulcerative colitis on clinical, radiological, and pathological evidence. The main features have already been described from the clinical, radiological, and pathological aspects, and it must be emphasized that the final distinction between Crohn's disease of the colon and ulcerative colitis does not rest on any one feature, macroscopic or microscopic, but on the overall appearance taken in conjunction with the clinical findings. In view of the difficulty in distinguishing between the two diseases, it may be helpful to emphasize the points of difference rather than the features which they possess in common.

In ulcerative colitis it is commonly the left side of the colon which shows the more advanced disease. Often the right side shows only relatively early changes and the caecum and ascending colon may often be normal in size or slightly dilated. On the other hand, a predominantly right-sided colitis with ileal involvement is more likely to be due to Crohn's disease than to ulcerative colitis, especially in the presence of a normal rectum. A particular point of distinction between the two diseases is that frequently in Crohn's disease the mucosal changes are discontinuous with areas of intervening normal mucosa, whereas in ulcerative colitis the disease is diffuse, although here again there may be a relatively normal area on the right side of the colon separating the diffuse disease on the left from an area of disease in the caecum. However, in cases of Crohn's disease one frequently sees small scattered ulcers throughout the bowel with areas of normal mucosa between them, and this is never seen in cases of ulcerative colitis, where if the ulcers are scattered, the mucosa between them is always abnormal, congested, and granular.

Microscopically, the main difference between Crohn's disease and ulcerative colitis is that in the former there is a granulomatous reaction extending through all layers of the bowel wall, whereas in colitis the inflammation is superficial and confined to the mucosa in the first place, with some later extension into the submucous tissue, but never any penetration of the muscularis externa except as the result of perforation in the acute fulminating form of the disease. Moreover, the intramural fissures of Crohn's disease are not seen in ulcerative colitis. Another important feature is that in cases of colitis the thickening of the bowel wall is due to muscular hypertrophy and spasm rather than to fibrosis (McGovern and Archer, 1957). Even in patients with a long history of severe and extensive ulcerative colitis, there is relatively little reactive fibrosis. There may be some increase in the submucous fibrous tissue but this is out of proportion to the intensity of the inflammation. On the other hand, Crohn's disease is very much a fibrous-tissue-producing condition and is classified among the chronic granulomatous diseases; and in cases of Crohn's disease of the colon considerable fibrosis can be found in the deeper layers of the bowel wall. However, the most striking histological feature which helps to differentiate the two diseases on microscopic examination is the giant-cell granuloma of Crohn's disease. It must be emphasized that these giant cells are not morphologically like foreign-body giant cells. Moreover, they are part of a giant-cell system and are not in any way isolated from their neighbouring cellular elements. They must be distinguished from the occasional foreign-body giant cell seen near the surface of the ulcers in chronic ulcerative colitis.

The distinction between chronic ulcerative colitis and Crohn's disease can sometimes be aided by rectal biopsy. In a few cases in this series a biopsy was taken from the rectum before operation and revealed non-caseating giant-cell systems in the rectal submucosa accompanied by a chronic

FIG. 19.—*Biopsy of a rectal lesion of diffuse Crohn's disease of the large intestine showing a granulomatous process in the submucosa with proliferation of epithelioid cells and a Langhams type giant cell.*

granulomatous reaction which was primarily submucous in its distribution (Fig. 19). The presence of giant-cell systems in a rectal biopsy should be reported as no more than suggestive of Crohn's disease and used in conjunction with other clinical and radiological features in contributing towards an accurate diagnosis. The histological examination of biopsy material from anal lesions such as ulcers, fissures, or fistulae, which commonly complicate Crohn's disease, will reveal non-caseating giant-cell systems identical with those found in the intestinal lesion in a high proportion of cases. In a previous paper (Morson and Lockhart-Mummery, 1959b) we have reported our experience with these anal lesions in cases of Crohn's disease. Although a few patients with chronic ulcerative colitis also develop anal lesions, the finding of giant-cell systems in anal biopsy material from a patient with inflammation of the large bowel may be helpful in distinguishing between chronic ulcerative colitis and involvement of the colon with Crohn's disease.

Ulcerative colitis and Crohn's disease of the large intestine have also to be distinguished from the ileo-colitis of Cooke and Brooke as well as from tuberculosis, and from certain cases of regional or segmental colitis as well as other specific diseases of the large intestine mentioned at the beginning of this paper. A special variety of "ileo-colitis" was first described by Brooke and Cooke in 1951 and again by the same authors in 1955 (Cooke and Brooke, 1955). The condition is characterized by diarrhoea, steatorrhea, and anaemia, with ulcers in the small bowel later spreading to involve the colon, extending from the ileo-caecal valve distally. At the moment the pathology of this condition is not clear and as an entity it is not fully accepted by gastro-

enterologists. Though tuberculosis affecting the ileo-caecal region is much rarer than Crohn's disease in this country, it may still occur (Thompson and Morson, 1958). Three such cases are reported by Pollock (1958) who draws attention to Anand's (1956) experience that giant-cell systems in the intestinal wall are not a constant feature of such cases, and that even if they do occur, central caseation in them is not the rule; Anand does say, however, that giant-cell systems with caseation are constantly found in the regional lymph nodes. These observations emphasize the importance of a careful search for caseation and tubercle bacilli in multiple sections of both the bowel wall and related lymph nodes before a certain diagnosis of Crohn's disease is given. "Regional" colitis is a difficult condition to define and has been the subject of many papers in the literature, and has recently been discussed by Watkinson and Goligher (1959). We believe that many cases that have been regarded as "regional colitis" are really examples of Crohn's disease, and many of those in our Group 2 and a few in Group 1 might have been so regarded. Nevertheless, there are still patients with localized lesions of the colon with no definite evidence of Crohn's disease which must, in the absence of more knowledge, be called for the time being "regional colitis". In the last year we have seen two such cases in clinical practice. One patient had a very localized fibrous stricture in the descending colon in which no specific histology was discovered, and the other had a 6 in. area of stenosis in the transverse colon with linear ulceration and with histology suggestive of ulcerative colitis, but with the rest of the bowel entirely normal. Cases such as this, and many of those in the paper reported by Watkinson and Goligher, must still be regarded as cases of "regional colitis", and in all of them the rectum was normal on sigmoidoscopy. We consider that this group of patients requires special study as it is likely that diseases of different pathology are still being grouped together under this heading.

We wish to thank the surgeons of St. Mark's Hospital for permission to use their case histories; also the staff of the Research Department for their help and to the Board of Governors of the Hammersmith and St. Mark's Group of Hospitals for a research grant.

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*Gut*, 1960, **1**, 106.

# VOLVULUS OF THE CAECUM

BY

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Three cases of volvulus of the caecum are presented and their symptoms and treatment are discussed. It is suggested that this condition may be commoner than is thought and would be diagnosed more frequently if considered in the differential diagnosis.

Volvulus of the alimentary tract accounts for 10% of all intestinal obstructions. It occurs most frequently in the sigmoid colon, less so in the small intestine and caecum, and least of all in the transverse colon. Whereas volvulus of the sigmoid colon is a well-known and well-documented entity, volvulus of the caecum is considered a rarity, a review of the literature published in English showing that only about 400 cases have been reported since Rokitanski's first case in 1839. Despite this, the three cases reported here were all seen inside five months in a general hospital of moderate size. This report is presented with the idea that perhaps this condition is much commoner than the textbooks suggest, and, if it is kept in mind, pre-operative diagnosis is possible and appropriate treatment may be started at an earlier stage than it usually has been.

## Case Reports

Case 1.—Mrs. L. W. is an old-age pensioner, aged 77, who was admitted to hospital on November 26, 1958, having had abdominal pain for 10 days. This pain was colicky in nature and worst in the left iliac fossa. She was nauseated and had anorexia but had not been vomiting, being able to keep down small amounts of water. She said that she was usually constipated and often passed no motions for three or four days, but she had passed none for eight days before admission; she had, however, been passing flatus each day. She had been quite well previously and had had no abdominal operations.

On examination Mrs. L. W. was a thin, dehydrated patient who was in no great pain. Her pulse rate was 100/minute and her blood pressure 190/100 mm./Hg. Examination of the heart and lungs showed no abnormality. The abdomen was distended symmetrically, being tender all over, the left side more than the right, but there was no rebound tenderness and no definite masses were felt. Bowel sounds were heard but were much reduced. Rectal examination revealed no abnormality, and repeated enemata yielded no result. A provisional diagnosis of obstruction of the large bowel by a carcinoma of the sigmoid colon was made, owing to the predominance of signs on the left side of the abdomen.

Intravenous therapy and continuous gastric aspiration were started.

Laparotomy that same evening showed a large volvulus of the caecum in an anticlockwise direction with one turn (360°) which had perforated in a very thinned-out area of anterior wall, releasing liquid faeces into the peritoneal cavity. Toilet was performed by mopping and sucking and the volvulus was untwisted. The perforation of the caecum was closed with mattress sutures and a caecostomy tube was sewn into the caecum with two purse string sutures and brought out through a loin stab incision. The main incision was closed in layers.

After operation the patient made a very good recovery, being kept on intravenous "achromycin" for three days. The caecostomy tube was removed on the eighteenth post-operative day and the stab wound closed quickly leaving no fistula. She was discharged from hospital on the thirty-fourth day (the long stay being partly due to social reasons) and when seen subsequently as an out-patient was well with no complaints.

Case 2.—Mr. T. D. is an unemployed man, aged 40, who was admitted from another hospital where he had been sent two weeks before having taken an overdose of "persomnia" tablets. He was treated for this overdosage with gastric washouts and was restored to health in 24 hours. He gave a history of a partial gastrectomy having been performed in 1956 for a duodenal ulcer.

On December 9, while still in this other hospital, the patient had a sudden onset of abdominal pain, colicky in nature, which came on about two hours after a large meal. He was found to have a distended abdomen and a "loop of bowel" was noted as felt just below the umbilicus. There was no tenderness or rebound tenderness and bowel sounds were heard: he was put on a fluid diet and observed. The following morning he vomited and it was noted that no flatus had been passed for 24 hours and that repeated enemata had no result. That evening his clinical condition was a little worse and he was getting dehydrated: the loop of bowel previously noted was still palpable and was now tender. He

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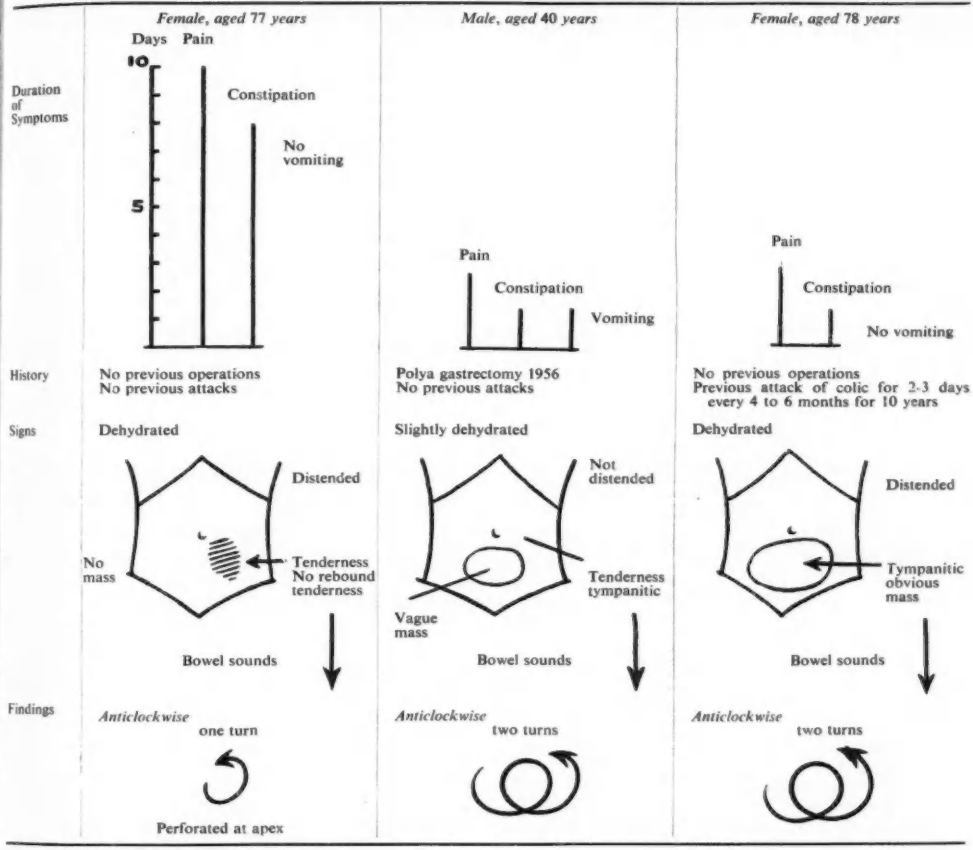
TABLE

SUMMARY OF FINDINGS IN THE THREE CASES




was therefore transferred to Edgware General Hospital.

At admission Mr. T. D. was a slightly built man who was moderately dehydrated but not in any acute pain. His pulse was 96/minute and his blood pressure was 150/85 mm. Hg.; examination of the heart and lungs showed no abnormality. The abdomen was distended and a tender, vague mass was felt below the umbilicus in the midline but there was no other tenderness and no rebound tenderness, the bowel sounds being slightly increased. Rectal examination revealed nothing abnormal. A provisional diagnosis of intestinal obstruction from gastrectomy adhesions was made and intravenous therapy and regular gastric aspirations were started. The following morning the dehydration had improved but the abdominal findings were unchanged and so laparotomy was performed.

At operation, the caecum, terminal ileum, and descending colon were involved in an anticlockwise volvulus of two turns (720°) passing upwards towards the left hypochondrium, the caecum itself being grossly distended and its wall very much thinned. The volvulus was unwound and the caecum decompressed by a caecostomy tube passed into the lumen, secured by two purse string sutures and brought out through a loin stab incision. The main incision was closed in layers.

The patient made a good post-operative recovery, the caecostomy working well from the start and the caecostomy tube came out of its own accord on the twelfth day, the caecostomy wound closing and leaving no fistula. The patient was discharged on the twenty-third post-operative day and when seen as an out-patient later was perfectly well.

CASE 3.—Miss J. B. is a miniature painter, aged 78, who was admitted on March 6 complaining of abdominal pain for four days. The pain was colicky and had

gradually worsened over the first two days, becoming more constant over the last two. Since the onset of pain she had diarrhoea for the first two days but no motions or flatus since then. She had not taken any food for the four days and had not vomited. She volunteered that she had had attacks of this sort of pain lasting two or three days every few months for 10 years and that they had always cleared spontaneously. She had had no abdominal operations and was vegetarian in her diet.

Examination showed a dehydrated, thin old lady; her pulse was 82/minute and blood pressure 150/100 mm. Hg. The heart and lungs were clinically normal. The abdomen was distended and tympanitic, a large obvious mass passing from the right iliac fossa towards and below the umbilicus. This was even more tympanitic than the rest of the abdomen. Occasional bowel sounds were heard and rectal examination revealed no abnormality. Repeated enemata yielded no result and intravenous therapy and gastric aspirations were started. A pre-operative diagnosis of volvulus of the caecum was made.

At laparotomy that evening an anticlockwise volvulus of the caecum, lower ascending colon, and the last 5 in. of ileum, with two turns (720°), was found. The volvulus was unwound and a caecostomy performed, the tube being secured by two purse string sutures to the caecal wall and brought out through a loin stab incision. The main incision was closed in layers.

Post-operative recovery was good, the patient being kept on intravenous "achromycin" for three days since there had been faecal soiling at operation. The caecostomy tube came out of its own accord on the tenth post-operative day and the patient was discharged on the twenty-ninth day.

## Discussion

The case histories of the three patients presented here show several interesting points when reviewed against the background of cases previously reported.

The aetiology of volvulus of the caecum is understood when the embryology of the region is remembered. Briefly, the midgut is formed from an endothelium-lined tube, the caecum being an outpocketing of it. During the third month of intrauterine life, after the gut has re-entered the peritoneal cavity and rotated around the axis of the superior mesenteric artery, the caecum begins to descend to the right iliac fossa where it is usually found by the time the infant is born. While the caecum is descending the mesentery of the ascending colon usually fuses with the parietal peritoneum of the posterior abdominal wall so that caecum and ascending colon are more or less bound down posteriorly.

In all these three cases, as in others reported, the caecum which had undergone volvulus was abnormally mobile due to deficient fixation during its descent into the right iliac fossa. The full range of movement of the caecum is well known, for commonly at appendicectomy it can be drawn out of the abdomen with ease. Several authors have demonstrated excessive mobility of the caecum; Wolfer, Beaton, and Anson (1942) found that in 14 out of 125 bodies the caecum was mobile enough to allow development of volvulus, the lack of fixation being more common in women than in men. Other series of figures show that the caecum has a wide range of mobility, between 10% and 20% of human caecums being highly mobile (Kantor and Schechter, 1934; Coughlin, 1927). As well as this predisposition there must be an additional factor to cause volvulus, otherwise the condition would be even commoner. Among such factors are constipation (as in Case 1), previous irritation of the peritoneum by inflammation or operations (as in Case 2), pregnancy, recent loss of body fat (Cases 1 and 3), and a coarse vegetable diet (Case 3). The final exciting cause is usually considered to be increased peristalsis, commonly after a heavy meal (as in Case 2), or after violent purging, although over-exertion and trauma have been cited.

Volvulus of the caecum has been reported in all age groups but is commonest in the young adult, more than half the cases occurring in patients between 20 and 40 years. In our three cases, however, the ages were 40, 70, and 77, the last patient being one of the oldest recorded to survive. Further, the volvulus is said to occur more frequently in males than in females despite the increased potential mobility of the female caecum.

Pathology.—It is usually considered that in order to produce pathological changes in intestine a volvulus must be of at least 180° on its mesenteric border. In this connexion, it is interesting to see that Ingelfinger (1942) in a radiological series showed that the normal caecum could in some people rotate through 180° just by stimulation of simple body movements and the patient did not complain of any symptoms. If, however, the rotation exceeded 180°, then colicky pain was experienced. In these three cases the degree of torsion was 720° in two and 360° in the other but it was the latter case which had perforated and so the actual amount of twist was not the sole initiating factor. It is the tightness of the twist of the mesentery (and its duration) rather than the number of times which determines the amount of vascular occlusion and whether gangrenous changes will follow. This is well shown in the patient described as Case 1 who had only one complete twist but had had symptoms for eight days.

A further consideration is the torsion of the gut itself. In a volvulus, the intestine is twisted in two places and so produces a closed loop obstruction. From this loop gas, which is produced by fermentation of large bowel contents, cannot escape and so

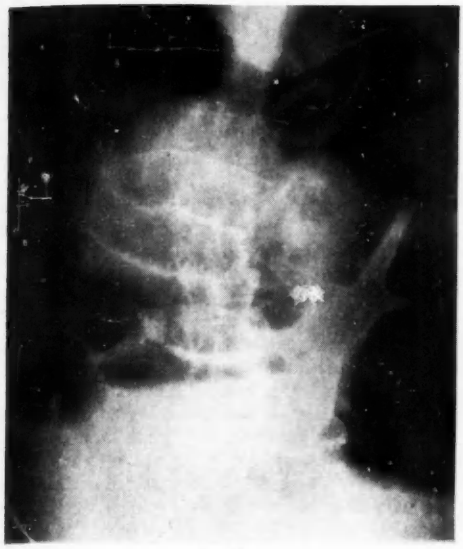


FIG. 1

FIG. 2a

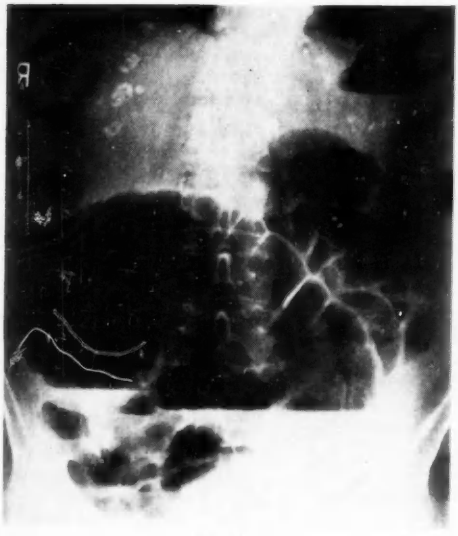


FIG. 3

FIG. 2b

FIG. 1.—*Erect view of abdomen showing grossly dilated loops of small bowel and free air under the diaphragm.*

FIG. 2.—*Views of abdomen, the patient lying flat and lying on the right side. There is a dilated loop of large bowel which falls over to the left, and a huge fluid level is seen when the patient lies on his side.*

FIG. 3.—*Erect view of abdomen showing a loop of large bowel twisted on itself arising from the right iliac fossa. Two separate fluid levels can be seen in the two limbs of the loop. (Shadows of calcified costal cartilages are seen in the upper part of the abdomen.)*

rapid distension may occur leading to a thinning of the caecal wall which is already ischaemic from blockage of its blood supply. This too may predispose towards perforation and faecal soiling of the peritoneum.

As well as the acute cases there would appear to be those patients who have an intermittent twisting which allows of a form of subacute obstruction. The subject of Case 3 showed this, for she told of attacks of pain for 10 years every few months which passed without treatment. In such cases the volvulus of the caecum obviously untwists spontaneously with complete relief of symptoms and may earn the patient the diagnosis of "subacute appendicitis" or "appendicular colic".

At operation in every case the twist was found to be anticlockwise. It has been previously stated that most cases had a clockwise twist but, as Wolfer *et al.* (1942) point out, it depends on the siting of the clock. It is obvious from some descriptions and diagrams that the clockwise twist is in relation to the observer whereas most recent reports relate the clock to the patient. Hence this apparent anomally may be one of nomenclature and the anticlockwise left-to-right volvulus may really be the commoner disease.

SYMPTOMS AND SIGNS.—The presenting symptoms were those of a lower small intestine obstruction. They may be acute and fulminating or more gradual, even resolving, as mentioned above. Case 1 had a 10-day history of gradually worsening obstruction whereas that of Case 2 was of only three days' symptoms starting suddenly after a heavy meal. Case 3 fell between these two, with four days' illness that had obviously only been severe for the last two days. Examination showed signs varying with the degree of obstruction and its duration but particular stress is placed on the abdominal distension and the tympanitic mass, which can often be felt arising from the right iliac fossa and passing towards the umbilicus or even to the left hypochondrium. This mass was felt at some stage in two of the three cases, its full significance not being fully appreciated in one of them until operation but in the other it led to the true diagnosis.

Radiographs were taken of the patient lying flat and standing up or in one case lying on his side (Case 2) soon after admission. They showed dilated loops of large bowel with caecal fluid levels in Cases 2 and 3. These confirmed the diagnosis of obstruction of the large bowel and in Case 3 aided the diagnosis of volvulus of the caecum.

TREATMENT.—The treatment of caecal volvulus is operative. Once dehydration and electrolyte imbalance have been corrected a laparotomy must be performed and subsequent procedures will then depend on the intra-abdominal findings and the patient's condition. If the caecum is viable and not very distended, simply untwisting may suffice. Because of the possibilities of recurrence it is advocated that the caecum be fixed to the abdominal wall. A simple manoeuvre is to remove the appendix and use one end of the purse string suture to fix the caecum to the anterior abdominal wall (Lyall, 1946). Should there be much distension a safer method is to perform a caecostomy by sewing into the lumen of the caecum a de Pezzer catheter with its tip amputated. By bringing this out of the abdomen through a separate loin incision, it both decompresses and later fixes the caecum by forming adhesions.

Should the caecum not be viable then either an exteriorization and excision should be performed leaving an ileostomy, or, if the patient's condition allows, a resection with ileo-transverse colostomy.

In all three cases it was considered that the distension warranted deflation before untwisting could be safely performed; further, after reduction of the caecum, it may be several days before normal peristalsis occurs in the damaged segment and distension must be avoided. Hence a caecostomy tube as described above, led out through a loin stab incision, was used in every case. In all cases the tube came out easily in the early post-operative period and the wound healed well with no faecal fistula.

The mortality in published cases of volvulus of the caecum is in the region of 50 to 60% (this includes cases reported before the days of antibiotics). One reason for this high figure may be the delay in operating because the diagnosis is not made.

In our three cases the pre-operative diagnoses were respectively: (1) Obstruction of the large gut due to carcinoma of the colon; (2) lower ileal obstruction due to adhesions; and (3) volvulus of the caecum. But it is most important to admit honestly that the last and correct diagnosis was only made because we had seen two similar cases recently and had it in mind. It is possible that caecal volvulus is a much commoner condition than was thought and, that being so, it should be considered in the differential diagnosis of intestinal obstruction more often, for it is a condition that responds well to treatment.

I wish to thank Mr. D. B. Craig, under whose care these patients were admitted, for his help and permission to publish these cases and to express my appreciation to Professor Ian Aird for his advice.

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*Gut*, 1960, **1**, 111.

# A TEST OF PANCREATIC FUNCTION IN MAN BASED ON THE ANALYSIS OF DUODENAL CONTENTS AFTER ADMINISTRATION OF SECRETIN AND PANCREOZYMIN

BY

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Pancreozymin in man as in animals appears to act as a specific enzyme stimulant. The preparations of pancreozymin used in these experiments also contain cholecystokinin, which causes the gall bladder to contract, and a smooth muscle stimulant, possibly substance P.

The duodenal contents obtained in response to a standard dose of secretin and pancreozymin have been collected quantitatively in man and the volume and amount of bicarbonate, amylase, trypsin, and lipase measured in order to study pancreatic function. The results of 105 tests undertaken on a normal group, in pancreatic and biliary disease, and in non-pancreatic steatorrhoea have been analysed.

In localized pancreatic lesions and after recovery from acute pancreatitis, normal function is often retained. Mild functional impairment may be demonstrated only by a poor enzyme output in the post-pancreozymin fractions, while at a later stage bicarbonate output is affected and finally the volume of the duodenal contents is reduced. The secretin-pancreozymin test is most valuable, therefore, in the more chronic and advanced forms of pancreatic disease in which it gives a good assessment of residual pancreatic function. In diagnosis care must be taken in interpreting a functional test in terms of anatomical pathology. The test has proved useful not only in diagnosis but also as a guide to treatment and an index of prognosis.

In 1902, Bayliss and Starling showed that extracts of duodenal mucosa contained a material, secretin, which on intravenous injection caused the pancreas to secrete. The earliest attempts to establish a test of pancreatic function in man by stimulating the pancreas with secretin were made in Chiray's clinic in Paris (Chiray, Salmon, and Mercier, 1926; Chiray, Jeandel, and Salmon, 1930; Bolgert, 1935). Voegtlin, Greengard, and Ivy (1934) in America and Voet (1943) in Belgium conducted similar experiments. It was not until Ågren and Lagerlöf (1936), who used a purified preparation of secretin, adopted the double lumen tube method of Lim, Matheson, and Schlapp (1923) to obtain uncontaminated specimens of duodenal juice that accurate quantitative measurements of pancreatic function could be made. Since that time the technique elaborated by Ågren and Lagerlöf has been closely followed by other workers and the value of the secretin test in assessing pancreatic function in man confirmed (Lagerlöf, 1939, 1942; Diamond, Siegel, Gall, and Karlen, 1939; Diamond and Siegel, 1940, 1941; Comfort and Osterberg, 1940; Pratt, Brugsch, and Rostler, 1940; Pollard, Miller, and Brewer, 1942; Lake, 1947; Dornberger, Comfort, Wollaeger, and Power, 1948; Dreiling and Hollander, 1948, 1950; Friedman and Snape, 1950; Dreiling, 1950, 1951, 1953, 1955; Dreiling and Janowitz, 1957; Wenger and Raskin, 1958).

In anaesthetized animals secretin produced a large volume of pancreatic juice of constant alkalinity and low enzyme content. Harper and Raper (1943) isolated from the small intestine a second material, other than secretin, which increased the enzyme output by the pancreas without affecting the volume of juice. This material they named pancreozymin. Crick, Harper, and Raper (1949) later published a revised method of preparing secretin and pancreozymin and preliminary experiments showed that pancreozymin had the same effect on man as in animals (Duncan, Harper, Howat,

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Oleesky, and Varley, 1950; Howat, 1952). In the present paper the effects produced by secretin and pancreozymin on the volume and composition of the duodenal contents in normal adults is described and compared with those in patients who have pancreatic disease.

When this work was started pancreozymin preparations were found to contain cholecystokinin (Ivy and Oldberg, 1928), which causes a contraction of the gall bladder in animals and man (Duncan, Evans, Harper, Howat, Oleesky, Scott, and Varley, 1953). A test of gall bladder function in man has been based on this property of the extracts (Duncan *et al.*, 1952; Burton, Harper, Howat, Scott, and Varley, 1960a).

## Methods

Secretin and Pancreozymin.—These were prepared from pig intestine according to the method of Crick *et al.* (1949). Aqueous solutions of secretin (2·5 mg./ml.) and of pancreozymin (7 mg./ml.) were sterilized by filtration through a "gradocol" membrane. The sterile solutions were then freeze-dried in ampoules. In this state both are pale yellow powders soluble in water. Stored in the dark at 4°C. they showed no appreciable loss of potency over two years.* Neither secretin nor pancreozymin produced any anaphylactic reactions in guinea-pigs, and no toxic effects were observed in mice following intravenous injections of secretin and pancreozymin in doses per kilogram/body weight up to 200 times those given to patients.

Varying amounts of secretin and pancreozymin, up to 2·5 units of both, have been given to 285 adult subjects, secretin alone to 16, and pancreozymin alone to 10. In most cases the dosage employed for both secretin and pancreozymin has been 1·7 units per kilogram of body weight. Immediately before use the extract is dissolved in pyrogen-free distilled water. Both preparations are given intravenously. The injection of secretin in 10 ml. of water can be completed within two minutes. After only two of 301 secretin injections (0·7%) has any untoward effect been noted. After pancreozymin, however, in a total of 295 injections, general symptoms have been experienced by 38 patients (13%). In only nine (3%) were reactions of even moderate severity encountered; in the others they were negligible and the subjects complained only on being questioned. The minor sensations were variously described as a flushing of the face, a hot head, clammy skin, nausea or sickliness, a sinking feeling in the upper abdomen. In the nine more severe instances the patients complained of faintness which was associated with slowing of the pulse. Reactions were of such severity as to warrant discontinuing the infusion on three occasions (1%). No allergic reactions were encountered but these biological preparations have not been given to asthmatic subjects. In a few instances patients complained of abdominal discomfort which resembled a bowel pain rather than a pain arising in the pancreas or gall bladder. One man, aged 59, who had a large incisional hernia of the abdomen and a large scrotal hernia, complained during the injection that his testicles were moving. Intense small bowel motor activity was observed for some 10 minutes in the hernial sacs. These effects on the vasomotor system and intestinal muscle are not caused by histamine or 5-hydroxytryptamine. They may be due to the presence in pancreozymin preparations of the vasodilator and plain muscle stimulant, substance P, which Euler and Gaddum (1931) have found in intestinal extracts. Jorpes and Mutt have recently succeeded in separating this material from the pancreozymin and cholecystokinin fractions of pancreczymin preparations (Hultman, 1955 a and b; Jorpes and Mutt, 1956, 1959).

In addition local pain in the arm at the site of injection or referred along the course of the vein was experienced by 16 patients (6% of the total). This was attributed to venous spasm. Thrombosis of a segment of an arm vein was encountered in seven patients (2·5%) following secretin and pancreozymin, a complication particularly liable to occur in patients with difficult veins, where recent intravenous fluids have been given, when numerous venepunctures were made and in patients with advanced malignant disease. All the untoward effects are aggravated by the rapid delivery of too concentrated solutions of pancreozymin. Since we adopted the technique of dissolving the required dose of pancreozymin in 16 to 20 ml. of distilled water and injecting it slowly in four or five minutes, reactions were reduced by two-thirds and were correspondingly milder. All reactions have been of a transient nature. There has been no suspicion that pancreatitis may have been induced or aggravated by giving either of these preparations.

Technique of Intubation.—In place of the two separate tubes, one in the stomach and the other in the duodenum which we used in our early experiments (Howat, 1952), we now pass a single radio-opaque double lumen tube weighted by a thin latex bag containing 1·5 ml. of mercury, which has proved less disagreeable to patients.

Two methods of intubation have been used.

(*a*) *Rapid Method.*—With the patient seated and inclining slightly forward, the tube is rapidly introduced through the mouth into the stomach to the 60 cm. mark. The patient then lies semi-prone on the right side and with the foot of the couch raised 35 cm., the tube is passed on to the pylorus, being guided and controlled by pressure of the flat hand and fingers on the anterior abdominal wall up towards the right costal margin. Once the distal end of the tube reaches the pylorus the tube is passed to 75 cm. When the tube enters the duodenum (in most instances in 25 to 30 minutes) the patient sits up or walks about. Adequate radioscopic control of this method is necessary at all stages.

(*b*) *Gradual Method.*—Late in the previous evening the tube is passed by mouth to the 60 cm. mark but no further. A barbiturate hypnotic is given, the foot of the

*Much of the secretin and pancreozymin used in this study has been provided by Boots Pure Drug Company, Limited, Nottingham.

bed is raised, and the patient is encouraged to sleep on the right side. No food is given but water is available until an hour before the test. On waking the tube is advanced to the 75 cm. mark. By morning the tube has entered the duodenum and its location in the alimentary tract is checked radioscopically and adjusted immediately before the test.

During the test the patient reclines on a couch with head and shoulders comfortably raised. Continuous suction at a negative pressure of from 25 to 40 mm.Hg is applied to both gastric and duodenal tubes. Salivary ejectors are used throughout the experiment. The technique of Ågren and Lagerlöf is followed, both gastric and duodenal contents being collected in successive 10-minute samples. After at least two control periods of 10 minutes each (specimens C1 and C2), the secretin is injected. Three 10-minute samples are collected in the next half hour (specimens D1, D2, and D3). Between the twenty-fifth and thirtieth minute after the secretin injection pancreozymin is injected and the aspiration continued for a further 30 minutes (specimens D4, D5, and D6), at the end of which the collection ends. If the volume recovered has been low (less than 150 ml./60 min.) or if the flow has been so delayed or capricious as to suggest incomplete aspiration of the duodenal contents, the position of the tube is again verified radioscopically after which the tube is withdrawn. The fractions of gastric and duodenal contents are collected in glass tubes surrounded by ice during the time of collection, and at the end of each 10-minute period the duodenal sample is diluted with an equal volume of glycerol and stored on ice to preserve the enzymes. Samples of blood for estimation of serum enzymes are collected before and at various intervals for 24 hours after giving secretin and pancreozymin. The results of the serum enzyme estimations are described in a paper by Burton, Hammond, Harper, Howat, Scott, and Varley (1960b).

CHEMICAL METHODS.—The volume of the duodenal contents is measured. Bicarbonate concentration is estimated by the gasometric method according to Peters and Van Slyke (1932). The concentration of amylase is determined by Lagerlöf's adaptation of the method of Nørby (Lagerlöf, 1942); of trypsin by the method of Gowenlock (1953); and of lipase by the method of Cherry and Crandall (1932). The outputs of bicarbonate and enzymes are obtained from the product of the concentrations and the volume of the samples. The icteric index of Meulengracht is used as a measure of the concentration of bile in the duodenal contents. In comparing the mean results in normal subjects with those in groups of patients the t test has been applied using the normal series only for the estimation of variance (Pearson and Hartley, 1954).

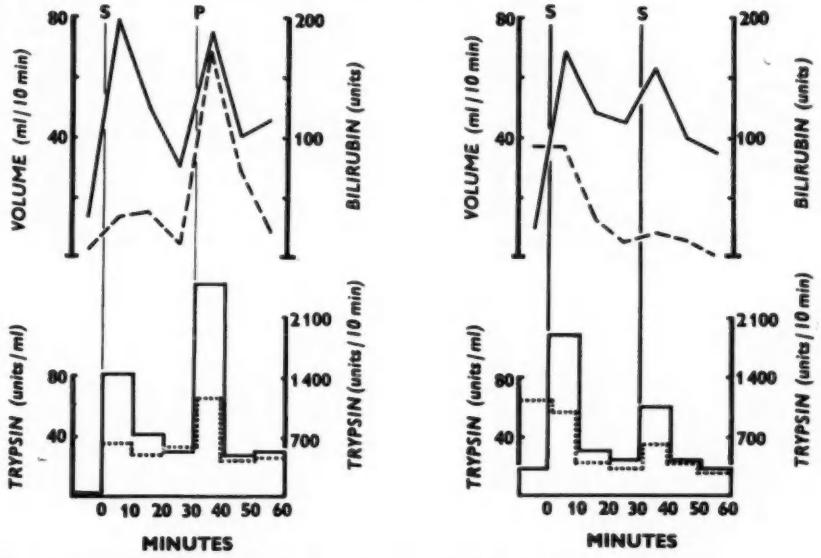


FIG. 1.—The Secretin-pancreozymin Test.—*The volume of duodenal contents, concentration of bilirubin, concentration and output of trypsin compared in two normal subjects (on left) in response to secretin (S) followed in 30 min. by pancreozymin (P) and (on right) in response to secretin (S) followed in 30 min. by a second equal injection of secretin (S).*

*Upper half*
——— *Volume (ml./10 min.)*
— — — *Bilirubin concentration (units)*
*Lower half*
- - - - - *Concentration of trypsin (units/ml.)*
——— *Output of trypsin (units/10 min.)*

## Results

Normal Pancreas.—In fasting man, when gastric contents are prevented from entering the duodenum, the volume of duodenal contents recovered in successive 10-minute samples falls to a low level. The fluid usually contains a moderate concentration of bile and only a little bicarbonate. On the other hand the enzymes—amylase, trypsin, and lipase—may be present in considerable concentration.

When secretin is given alone the volume of the duodenal aspirate increases rapidly in the first 10 minutes and then gradually falls over the next 50 minutes. When pancreozymin is given 30 minutes after secretin the output of duodenal contents again increases. This increase is associated with the appearance of gall bladder bile in the fluid and is largely due to the cholecystokinin in pancreozymin extracts causing partial emptying of the gall bladder (Fig. 1).

With the outpouring of fluid after the injection of secretin the concentration of bicarbonate also rises but reaches a maximum more slowly than the volume, usually in the third 10-minute fraction (specimen D3). This sample is frequently colourless showing absence of admixture with bile, and in composition approaches more nearly to pure pancreatic juice than any other sample. There is a fall in the bicarbonate concentration when the gall bladder empties following pancreozymin although the output of bicarbonate in the first specimen after pancreozymin (D4) is increased. In the final samples (D5 and D6) bicarbonate output diminishes as the volume diminishes (Fig. 3).

In healthy man the three pancreatic enzymes are secreted in parallel fashion by the pancreas. The concentration and output of enzymes increase after the administration of secretin (in specimen D1) and then fall to a low level. There is a comparable peak in concentration and output of enzymes in the first post-pancreozymin sample (D4). The rise after secretin is due to an outpouring of enzyme in the first five minutes of the test and is probably due to the washing out of enzymes from the ducts of the resting gland by the flow of secretin-stimulated juice. The increase in output of the enzymes (concentration × volume) which follows the dosage of pancreozymin given in this test is of the same order of magnitude as that which follows secretin. If a second injection of secretin is substituted for pancreozymin a rise in volume follows due to a further outpouring of pancreatic juice, but the increased output of bile and enzymes, characteristic of the response to pancreozymin preparations, is absent (Fig. 1).

The test was carried out in 21 normal adult

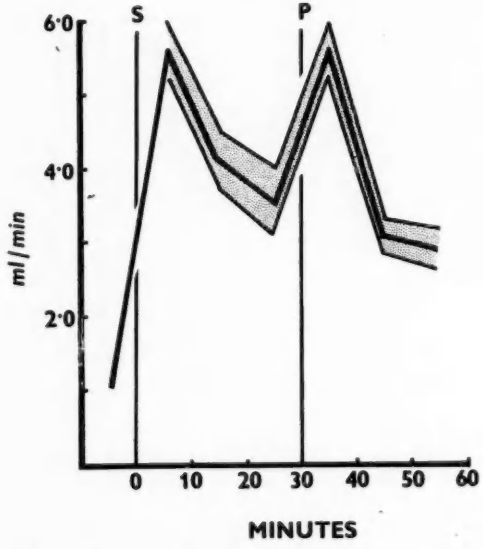


Fig. 2.—The Secretin-pancreozymin Test.—*The mean volume of duodenal contents ± 2 S.E. of mean in 21 normal subjects (ml./min.).*

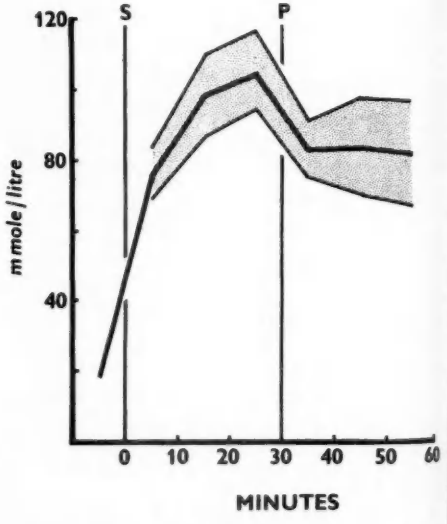


Fig. 3.—The Secretin-pancreozymin Test.—*The mean concentration of bicarbonate ± 2 S.E. of mean in 18 normal subjects (m.mole/litre).*

subjects, a group made up of 16 healthy medical students, aged 21 to 27 years, and five patients aged 35 to 63 years, in whom the liver, gall bladder, and pancreas were known to be normal. The mean volumes and the mean concentration and outputs of bicarbonate, amylase, trypsin, and lipase for this group are shown in Tables I and II and Figs. 2, 3, 4, and 5. The standard errors of the mean total volume and bicarbonate output are about 5% of the mean. On the other hand, the standard errors of the mean outputs of amylase, trypsin, and lipase are each about 10% of the mean, which seems to indicate either a greater variability in the output of these enzymes or an inherently greater error in the methods of estimating enzyme activities than in the method of measuring bicarbonate. The variances of the means of the samples collected immediately after secretin and pancreozymin (samples D1 and D4) have been compared by calculating the variance ratio of these two samples. There was no significant difference between the variances for the volume, bicarbonate output, or lipase output in the samples, but the variance after pancreozymin was significantly less than after secretin for amylase output ($P<0.05$). and for trypsin output ($P<0.001$). We interpret this as an indication of the greater variation in the amylase and trypsin content of the dead space in the resting gland which is washed out by secretin

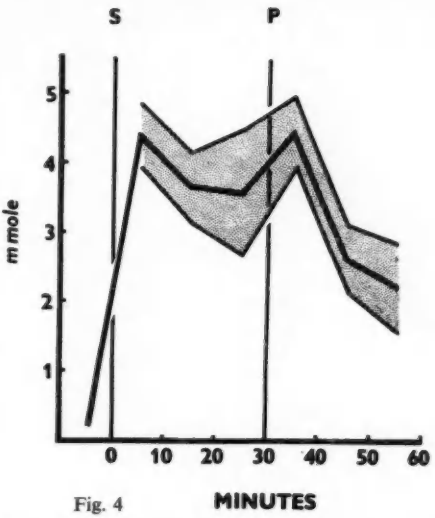


Fig. 4

FIG. 4.—The Secretin-pancreozymin Test.—*The mean output of bicarbonate ± 2 S.E. of mean in 18 normal subjects (m.moles).*

FIG. 5.—The Secretin-pancreozymin Test.—*The mean output of amylase, trypsin, and lipase in 20 normal subjects graphed to show the parallelism of enzyme output.*

———— *Amylase (Norby units)*
– – – – – – – – *Trypsin (Gownelock units)*
—— —— —— *Lipase (Cherry & Crandall units ÷ $10^2$)*

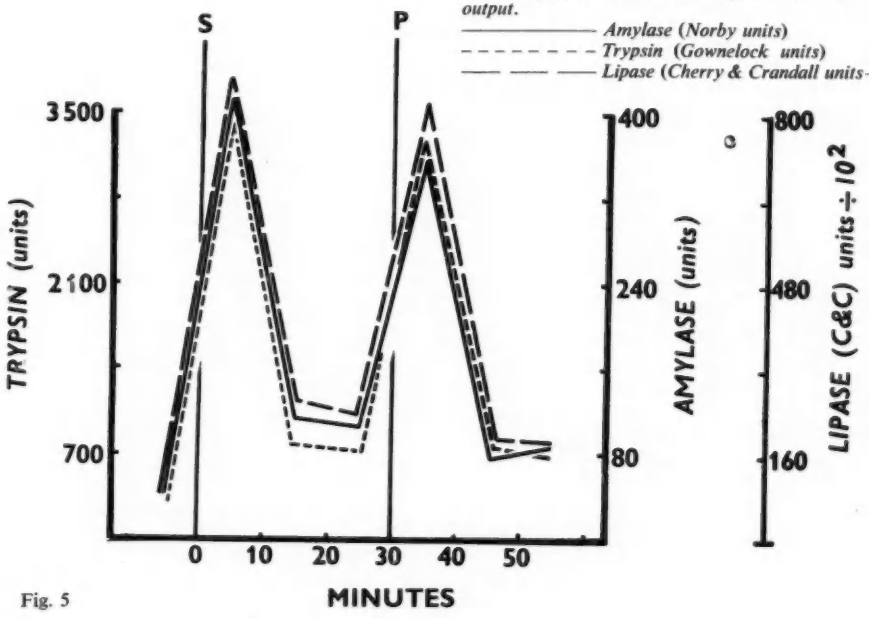


Fig. 5

## TABLE I

### VOLUME AND BICARBONATE AFTER SECRETIN AND PANCREOZYMIN

| Group (and No. of Cases) | Mean Concentration (Samples) | | | | | | | Mean Output (Samples) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C2 | D1 | D2 | D3 | D4 | D5 | D6 | C2 | D1 | D2 | D3 | D4 | D5 | D6 | Post-secretin (D1–3) | Post-pancreozymin (D4–6) | Total (D1–6) | Output /kg. |
| | Volume (ml.) | | | | | | | | | | | | | | | | | |
| Normal (21) | | | | | | | | 10 | 57 | 42 | 36 | 57 | 31 | 28 | 135 | 116 | 251 | 3·75 |
| S.D. | | | | | | | | 21·30 | 18·19 | 17·09 | 20·65 | 16·03 | 10·39 | 12·31 | 28·57 | 28·27 | 50·18 | 0·76 |
| S.E. | | | | | | | | 4·60 | 3·97 | 3·73 | 4·51 | 3·50 | 2·27 | 2·69 | 6·24 | 6·17 | 10·95 | 0·16 |
| Carcinoma of pancreas | | | | | | | | | | | | | | | | | | |
| Total (17) | | | | | | | | 3 | 22 | 23 | 19 | 27 | 18 | 13 | 63 | 57 | 121 | 2·2 |
| Normal vol. (7) | | | | | | | | 3 | 41 | 48 | 40 | 46 | 37 | 26 | 129 | 108 | 237 | 4·5 |
| Reduced vol. (10) | | | | | | | | 2·5 | 9·0 | 4·9 | 3·6 | 13·6 | 4·6 | 3·5 | 17·5 | 21·7 | 39·2 | 0·74 |
| Post-acute pancreatitis | | | | | | | | | | | | | | | | | | |
| Total (14) | | | | | | | | 7 | 66 | 48 | 43 | 53 | 33 | 25 | 156 | 110 | 267 | 4·2 |
| Chronic pancreatitis | | | | | | | | | | | | | | | | | | |
| Total (15) | | | | | | | | 5·4 | 34 | 23 | 19 | 40 | 15 | 16 | 76 | 71 | 147 | 2·7 |
| Normal vol. (7) | | | | | | | | 6 | 46 | 36 | 31 | 69 | 25 | 22 | 114 | 115 | 229 | 4·96 |
| Reduced vol. (8) | | | | | | | | 5 | 24 | 11 | 8 | 14 | 8 | 11 | 43 | 32 | 75 | 1·51 |
| Gall-bladder disease | | | | | | | | | | | | | | | | | | |
| Total (27) | | | | | | | | 7 | 52 | 45 | 38 | 49 | 28 | 29 | 135 | 105 | 240 | 4·23 |
| | Bicarbonate (m.Mole/100 ml.) | | | | | | | m.Moles | | | | | | | | | | |
| Normal | 1·80 | 7·53 | 9·82 | 10·47 | 8·30 | 8·32 | 8·17 | 0·16 | 4·36 | 3·61 | 3·56 | 4·46 | 2·57 | 2·20 | 11·35 | 8·90 | 20·26 | 0·31 |
| S.D. | 2·88 | 1·54 | 2·50 | 2·29 | 1·72 | 2·64 | 3·04 | 0·21 | 0·96 | 1·07 | 1·92 | 1·09 | 1·01 | 1·27 | 2·55 | 2·50 | 4·51 | 0·066 |
| S.E. | 0·87 | 0·37 | 0·59 | 0·54 | 0·40 | 0·66 | 0·76 | 0·06 | 0·23 | 0·25 | 0·45 | 0·26 | 0·25 | 0·32 | 0·60 | 0·59 | 1·06 | 0·015 |
| Carcinoma of pancreas | 0·31 | 3·47 | 6·00 | 5·68 | 5·17 | 5·40 | 4·99 | 0·01 | 1·33 | 2·38 | 1·69 | 1·75 | 1·29 | 1·09 | 4·94 | 3·68 | 8·29 | 0·149 |
| Normal vol. | 0·33 | 4·76 | 7·48 | 7·82 | 6·59 | 7·06 | 7·07 | 0·01 | 2·28 | 3·81 | 2·97 | 3·03 | 2·39 | 1·74 | 9·07 | 7·00 | 16·00 | 0·295 |
| Reduced vol. | 0·28 | 2·18 | 3·74 | 3·19 | 3·93 | 3·70 | 1·90 | | 0·37 | 0·36 | 0·20 | 0·63 | 0·20 | 0·13 | 0·80 | 0·84 | 1·54 | 0·05 |
| Post-acute pancreatitis | 2·30 | 6·80 | 9·00 | 9·20 | 8·30 | 7·90 | 7·50 | 0·18 | 4·40 | 4·30 | 4·00 | 4·50 | 2·65 | 1·90 | 12·60 | 9·10 | 21·70 | 0·34 |
| Chronic pancreatitis | 1·20 | 3·40 | 5·00 | 5·60 | 4·30 | 4·70 | 3·80 | 0·11 | 1·41 | 1·60 | 1·40 | 2·40 | 1·08 | 0·88 | 3·80 | 4·00 | 7·55 | 0·13 |
| Normal vol. | 1·31 | 4·55 | 6·55 | 7·07 | 5·94 | 6·23 | 5·50 | 0·11 | 2·23 | 2·44 | 2·22 | 3·94 | 1·61 | 1·34 | 6·88 | 6·89 | 13·77 | 0·26 |
| Reduced vol. | 1·08 | 2·34 | 3·10 | 3·52 | 2·43 | 2·55 | 1·84 | 0·11 | 0·59 | 0·44 | 0·44 | 0·67 | 0·33 | 0·35 | 1·13 | 1·11 | 2·10 | 0·04 |
| Gall-bladder disease | 1·90 | 6·00 | 8·00 | 8·18 | 8·30 | 7·40 | 6·90 | 0·34 | 3·20 | 3·50 | 3·20 | 4·10 | 2·10 | 2·10 | 9·90 | 8·25 | 18·10 | 0·35 |

## TABLE II

### AMYLASE, TRYPSIN, AND LIPASE AFTER SECRETIN AND PANCREOZYMIN

| Group | Mean Concentration (Samples) | | | | | | | Mean Output (Samples) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C2 | D1 | D2 | D3 | D4 | D5 | D6 | C2 | D1 | D2 | D3 | D4 | D5 | D6 | Post-secretin (D1–3) | Post-pancreozymin (D4–6) | Total (D1–6) | Output /kg. |
| | Amylase (Nørby units/ml.) | | | | | | | Nørby Units | | | | | | | | | | |
| Normal | 5·66 | 7·98 | 2·94 | 2·87 | 6·48 | 2·60 | 2·92 | 42 | 411 | 110 | 104 | 358 | 76 | 91 | 624 | 525 | 1,148 | 17·3 |
| S.D. | 5·43 | 4·08 | 1·69 | 1·06 | 3·35 | 1·12 | 1·24 | 227 | 261 | 68 | 65 | 163 | 42 | 56 | 303 | 197 | 453 | 6·9 |
| S.E. | 1·32 | 0·96 | 0·40 | 0·24 | 0·75 | 0·26 | 0·28 | 15·1 | 59·8 | 15·7 | 14·6 | 36·4 | 9·3 | 12·5 | 67·8 | 44·0 | 101 | 1·5 |
| Carcinoma of pancreas | 4·74 | 3·12 | 1·29 | 0·90 | 1·46 | 1·20 | 1·28 | 12 | 106 | 47 | 28 | 56 | 31 | 27 | 170 | 110 | 270 | 5·1 |
| Normal vol. | 6·65 | 5·10 | 1·81 | 1·28 | 2·00 | 1·63 | 1·50 | 12 | 184 | 84 | 53 | 103 | 63 | 48 | 321 | 214 | 535 | 10·1 |
| Reduced vol. | 2·50 | 1·15 | 0·70 | 0·52 | 1·00 | 0·83 | 0·97 | | 16 | 4 | 2 | 15 | 3 | 3 | 20 | 20 | 37 | 0·7 |
| Post-acute pancreatitis | 12·36 | 6·12 | 2·60 | 2·50 | 4·80 | 3·10 | 3·00 | 88 | 383 | 121 | 111 | 240 | 101 | 73 | 615 | 414 | 1,029 | 16·0 |
| Chronic pancreatitis | 3·00 | 2·75 | 1·87 | 1·84 | 2·08 | 1·73 | 1·88 | 18 | 95 | 38 | 32 | 102 | 34 | 32 | 162 | 160 | 290 | 5·1 |
| Normal vol. | 4·45 | 3·14 | 1·80 | 1·59 | 2·45 | 2·23 | 1·84 | 24·5 | 153 | 64 | 48 | 156 | 57 | 34 | 264 | 247 | 511 | 8·8 |
| Reduced vol. | 0·84 | 2·37 | 1·94 | 2·13 | 1·57 | 1·14 | 1·93 | 9 | 37 | 11 | 14 | 27 | 7 | 29 | 60 | 59 | 97 | 1·6 |
| Gall-bladder disease | 6·50 | 5·88 | 2·65 | 2·90 | 4·80 | 2·90 | 2·80 | 51 | 280 | 113 | 104 | 219 | 74 | 70 | 497 | 362 | 859 | 16·0 |
| | Trypsin (Gowenlock units/ml.) | | | | | | | Gowenlock Units | | | | | | | | | | |
| Normal | 41 | 57 | 21 | 22 | 59 | 25 | 22 | 332 | 3,494 | 804 | 736 | 3,259 | 798 | 675 | 5,198 | 4,715 | 9,884 | 152 |
| S.D. | 31·34 | 26·61 | 10·04 | 8·82 | 22·37 | 9·72 | 10·54 | 249 | 2,180 | 517 | 414 | 1,146 | 490 | 468 | 2,743 | 1,583 | 3,822 | 61 |
| S.E. | 8·69 | 6·10 | 2·25 | 1·97 | 5·00 | 2·17 | 2·36 | 69 | 500 | 116 | 93 | 256 | 110 | 105 | 647 | 363 | 927 | 15 |
| Carcinoma of pancreas | 47 | 37 | 17 | 12·5 | 18 | 21 | 19 | 156 | 1,343 | 662 | 448 | 834 | 648 | 483 | 2,492 | 1,990 | 3,547 | 63 |
| Normal vol. | 50 | 46 | 20 | 16 | 25 | 24·5 | 22 | 174 | 1,902 | 970 | 739 | 1,412 | 883 | 668 | 3,612 | 2,962 | 6,574 | 116 |
| Reduced vol. | 41 | 21 | 11 | 8 | 10 | 12 | 10 | 102 | 365 | 123 | 40 | 160 | 100 | 52 | 534 | 289 | 521 | 10 |
| Post-acute pancreatitis | 58 | 57 | 27 | 25 | 42 | 30 | 27 | 529 | 3,530 | 1,259 | 1,089 | 2,256 | 906 | 618 | 5,878 | 3,779 | 9,658 | 156 |
| Chronic pancreatitis | 25 | 27 | 17 | 18 | 25 | 24 | 19 | 182 | 1,032 | 499 | 471 | 1,258 | 527 | 395 | 1,772 | 2,109 | 3,600 | 63 |
| Normal vol. | 50 | 37 | 23 | 24 | 37 | 35 | 28 | 281 | 1,786 | 858 | 703 | 2,077 | 817 | 563 | 3,347 | 3,457 | 6,804 | 119 |
| Reduced vol. | 11 | 16 | 10 | 10 | 11 | 9 | 7 | 107 | 277 | 80 | 146 | 303 | 121 | 158 | 394 | 536 | 796 | 14 |
| Gall-bladder disease | 46 | 47 | 23 | 26 | 41·5 | 26 | 22·5 | 392 | 2,490 | 965 | 1,014 | 2,134 | 755 | 638 | 4,468 | 3,501 | 7,969 | 141 |
| | Lipase (Cherry & Crandall units/ml.) | | | | | | | Cherry & Crandall Units ÷ 100 | | | | | | | | | | |
| Normal | 848 | 1,384 | 658 | 671 | 1,389 | 555 | 570 | 89 | 855 | 269 | 236 | 820 | 182 | 170 | 1,321 | 1,172 | 2,494 | 37 |
| S.D. | 680 | 575 | 300 | 212 | 461 | 280 | 196 | 104 | 469 | 155 | 97 | 373 | 121 | 102 | 656 | 476 | 1,052 | 17 |
| S.E. | 189 | 136 | 71 | 49 | 106 | 64 | 45 | 29 | 110 | 37 | 22 | 86 | 28 | 23 | 151 | 109 | 241 | 4 |
| Carcinoma of pancreas | 307 | 465 | 282 | 181 | 285 | 263 | 241 | 11 | 165 | 128 | 60 | 141 | 91 | 65 | 331 | 266 | 571 | 10 |
| Normal vol. | 516 | 714 | 336 | 249 | 455 | 356 | 329 | 18 | 267 | 160 | 89 | 254 | 127 | 100 | 546 | 481 | 1,025 | 18 |
| Reduced vol. | 29 | 116 | 92 | 60 | 86 | 46 | 86 | 2 | 22 | 15 | 10 | 9 | 6 | 4 | 30 | 15 | 40 | 0·6 |
| Post-acute pancreatitis | 1,108 | 1,082 | 492 | 388 | 745 | 454 | 398 | 88 | 675 | 235 | 169 | 404 | 165 | 105 | 1,080 | 674 | 1,754 | 28 |
| Chronic pancreatitis | 287 | 469 | 243 | 235 | 493 | 251 | 193 | 31 | 205 | 66 | 67 | 240 | 65 | 35 | 284 | 307 | 549 | 9 |
| Normal vol. | 394 | 641 | 280 | 291 | 603 | 369 | 259 | 36 | 333 | 106 | 101 | 349 | 99 | 53 | 540 | 501 | 1,041 | 18 |
| Reduced vol. | 206 | 269 | 191 | 137 | 338 | 45 | 39 | 27 | 55 | 10 | 19 | 89 | 4 | 5 | 59 | 80 | 119 | 2 |
| Gall-bladder disease | 982 | 1,060 | 434 | 492 | 820 | 479 | 382 | 105 | 538 | 187 | 194 | 407 | 157 | 120 | 919 | 681 | 1,600 | 28 |

(which itself does not stimulate enzyme production) compared with the active enzyme secretion after a standard dose of pancreozymin.

CANCER OF THE PANCREAS.—The secretin and pancreozymin test was performed on 17 patients with proved cancer of the pancreas, in 12 of whom the cancer was in the head, two in the body, two diffusely infiltrating the head and body of the pancreas, and one cancer of the ampulla of Vater.

The mean results of these cases are shown in Tables I and II. Characteristic of this group is a reduction in the volume of duodenal contents recovered, due partly to obstruction of the pancreatic ducts and partly to secondary obstruction of the bile ducts when they become involved in growth (Fig. 6). The mean concentration of bicarbonate and enzymes is reduced, the reduction of the concentration of all the enzymes being most marked in the immediate post-pancreozymin fraction (D4). Since the mean output of duodenal contents is so small, the total outputs of bicarbonate and enzymes are all very significantly diminished.

However, in seven of the 17 cases the individual total volumes were not significantly reduced and the mean bicarbonate and enzyme outputs of these

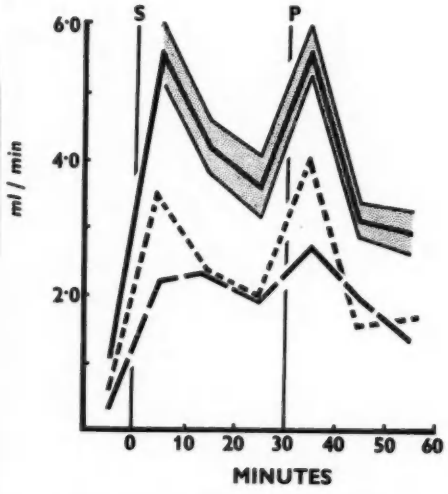


FIG. 6.—The Secretin-pancreozymin Test.—*A comparison of the mean volume of duodenal contents (ml./min.) in 21 normal subjects, in 21 patients with cancer of pancreas, and in 15 patients with chronic pancreatitis.*

In Figs. 6, 7 and 8 ———— *Normal ± 2 S.E. of mean*
———— ———— *Cancer of pancreas*
– – – – – – – – *Chronic pancreatitis*

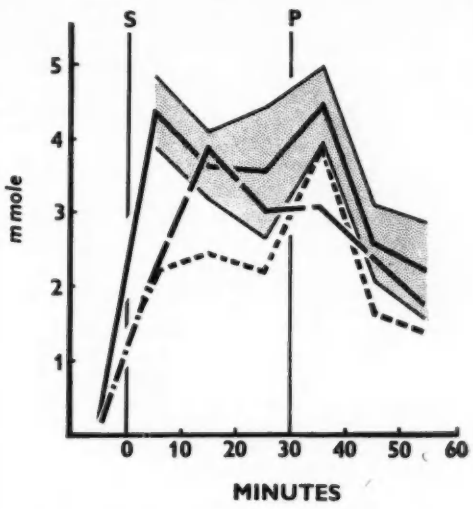


FIG. 7.—The Secretin-pancreozymin Test.—*A comparison of the mean output of bicarbonate (m.moles) in 18 normal subjects, in seven patients with cancer of the pancreas but normal volume response, and in seven patients with chronic pancreatitis but normal volume response.*

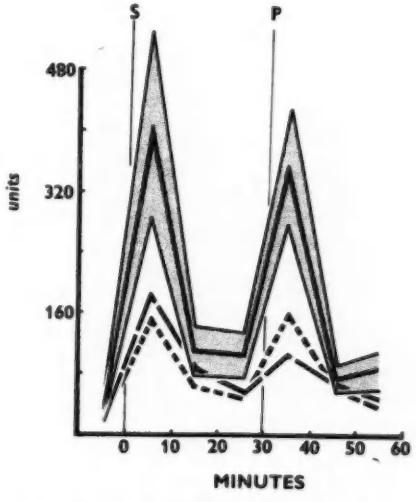


FIG. 8.—The Secretin-pancreozymin Test.—*A comparison of the mean amylase output in 20 normal patients, in seven patients with cancer of the pancreas with normal volume response, and in seven patients with chronic pancreatitis but normal response.*

TABLE III

MEANS AND SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS OF NORMAL AND ABNORMAL GROUPS

| Group (and No. of Cases) | Post-secretin Period (D1–3) | | | Post-pancreozymin Period (D4–6) | | | Total Output (D1–6) | | | Output/kg. Body Weight | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | S.D. & S.E. or t | P | Mean | S.D. & S.E. or t | P | Mean | S.D. & S.E. or t | P | Mean | S.D. & S.E. or t | P |
| | Volume (ml.) | | | | | | | | | | | |
| Normal (21) | 135 | S.D. 28·6<br>S.E. 6·2 | | 116 | S.D. 28·3<br>S.E. 6·2 | | 251 | S.D. 50·2<br>S.E. 10·95 | | 3·75 | S.D. 0·76<br>S.E. 0·16 | |
| | | t | | | t | | | t | | | t | |
| Carcinoma of pancreas | | | | | | | | | | | | |
| Total (17) | 63 | 7·716 | <0·001 | 57 | 6·392 | <0·001 | 121 | 7·932 | <0·001 | 2·20 | 6·252 | <0·001 |
| Normal vol. (7) | 129 | 2·006 | Not. sig. | 108 | | N.T. | 237 | | N.T. | 4·30 | 1·659 | Not sig. |
| Post-acute pancreatitis (14) | 156 | 2·13 | <0·05>0·02* | 110 | | N.T. | 267 | | N.T. | 4·20 | 1·716 | Not sig. |
| Chronic pancreatitis | | | | | | | | | | | | |
| Total (15) | 76 | 6·102 | <0·001 | 71 | 4·703 | <0·001 | 147 | 6·128 | <0·001 | 2·70 | 4·087 | <0·001 |
| Normal vol. (7) | 114 | 1·682 | Not sig. | 115 | | N.T. | 229 | 1·245 | Not sig. | 4·04 | | N.T. |
| Gall-bladder disease (27) | 135 | | N.T. | 105 | | N.T. | 240 | | N.T. | 4·23 | 2·135 | <0·05<0·02 |
| | Bicarbonate (m.Moles) | | | | | | | | | | | |
| Normal | 11·35 | S.D. 2·55<br>S.E. 0·60 | | 8·90 | S.D. 2·50<br>S.E. 0·59 | | 20·26 | S.D. 4·51<br>S.E. 1·06 | | 0·31 | S.D. 0·066<br>S.E.0·0015 | |
| | | t | | | t | | | t | | | t | |
| Carcinoma of pancreas | | | | | | | | | | | | |
| Total | 4·94 | 7·055 | <0·001 | 3·60 | 6·064 | <0·001 | 8·29 | 7·593 | <0·001 | 0·15 | 6·934 | <0·001 |
| Normal vol. | 9·07 | 2·006 | Not sig. | 7·00 | 1·706 | Not sig. | 16·00 | 2·119 | <0·05>0·02 | 0·285 | | N.T. |
| Post-acute pancreatitis | 12·60 | | | 9·10 | | N.T. | 21·70 | | N.T. | 0·34 | | N.T. |
| Chronic pancreatitis | | | | | | | | | | | | |
| Total | 3·80 | 8·470 | <0·001 | 4·00 | 5·507 | <0·001 | 7·55 | 8·056 | <0·001 | 0·13 | 7·803 | <0·001 |
| Normal vol. | 6·88 | 3·934 | <0·01>0·001 | 6·89 | 1·805 | Not sig. | 13·77 | 3·24 | <0·01>0·001 | 0·24 | 2·381 | <0·05>0·02 |
| Gall-bladder disease | 9·90 | | N.T. | 8·25 | | N.T. | 18·10 | 1·55 | Not sig. | 0·32 | | N.T. |
| | Amylase (Nørby Units) | | | | | | | | | | | |
| Normal | 624 | S.D. 303<br>S.E. 68 | | 525 | S.D. 197<br>S.E. 44 | | 1,148 | S.D. 453<br>S.E. 101 | | 17·3 | S.D. 6·9<br>S.E. 1·5 | |
| | | t | | | t | | | t | | | t | |
| Carcinoma of pancreas | | | | | | | | | | | | |
| Total | 170 | 4·301 | <0·001 | 110 | 6·094 | <0·001 | 270 | 5·556 | <0·001 | 5·1 | 5·178 | <0·001 |
| Normal vol. | 321 | 2·643 | <0·02>0·01 | 214 | 3·595 | <0·01>0·001 | 535 | 3·082 | <0·01>0·001 | 10·1 | 2·376 | <0·05>0·02 |
| Post-acute pancreatitis | 615 | | N.T. | 414 | 1·617 | Not sig. | 1,029 | | N.T. | 16·0 | | N.T. |
| Chronic pancreatitis | | | | | | | | | | | | |
| Total | 162 | 4·375 | <0·001 | 160 | 5·360 | <0·001 | 290 | 5·480 | <0·001 | 5·1 | 5·178 | <0·001 |
| Normal vol. | 264 | 2·706 | <0·02>0·01 | 247 | 3·213 | <0·01>0·001 | 511 | 3·202 | <0·01>0·001 | 8·8 | 2·805 | <0·02>0·01 |
| Gall-bladder disease | 497 | 1·397 | Not sig. | 362 | 2·758 | <0·02>0·01 | 859 | 2·126 | <0·05>0·02 | 16·0 | | N.T. |
| | Trypsin (Gowenlock Units) | | | | | | | | | | | |
| Normal | 5,198 | S.D. 2743<br>S.E. 647 | | 4,715 | S.D. 1583<br>S.E. 363 | | 9,884 | S.D. 3822<br>S.E. 927 | | 152 | S.D. 61<br>S.E. 15 | |
| | | t | | | t | | | t | | | t | |
| Carcinoma of pancreas | | | | | | | | | | | | |
| Total | 2,492 | 2·577 | <0·02>0·01 | 1,990 | 4·543 | <0·001 | 3,547 | 4·595 | <0·001 | 63 | 4·043 | <0·001 |
| Normal vol. | 3,612 | 1·298 | Not sig. | 2,962 | 2·504 | <0·05>0·02 | 6,574 | 1·929 | Not sig. | 116 | 1·314 | Not sig. |
| Post-acute pancreatitis | 5,878 | | N.T. | 3,779 | 1·679 | Not sig. | 9,658 | | N.T. | 156 | | N.T. |
| Chronic pancreatitis | | | | | | | | | | | | |
| Total | 1,772 | 3·572 | <0·01>0·001 | 2,109 | 4·574 | <0·001 | 3,600 | 4·641 | <0·001 | 63 | 4·119 | <0·001 |
| Normal vol. | 3,347 | 1·515 | Not sig. | 3,457 | 1·797 | Not sig. | 6,804 | 1·795 | Not sig. | 119 | 1·205 | Not sig. |
| Gall-bladder disease | 4,468 | | N.T. | 3,501 | 2·520 | <0·05>0·02 | 7,969 | 1·593 | Not sig. | 141 | | N.T. |
| | Lipase (Cherry & Crandall Units ÷ 100) | | | | | | | | | | | |
| Normal | 1,321 | S.D. 656<br>S.E. 151 | | 1,172 | S.E. 476<br>S.E. 109 | | 2,494 | S.D. 1052<br>S.E. 241 | | 37·2 | S.D. 16·9<br>S.E. 3·9 | |
| | | t | | | t | | | t | | | t | |
| Carcinoma of pancreas | | | | 266 | | | | | | | | |
| Total | 331 | 4·093 | <0·001 | 481 | 5·473 | <0·001 | 570 | 5·083 | <0·001 | 10·2 | 4·414 | <0·001 |
| Normal vol. | 546 | 2·673 | <0·02>0·01 | 674 | 3·284 | <0·01>0·001 | 1,025 | 3·161 | <0·01>0·001 | 18·4 | 2·528 | <0·02 |
| Post-acute pancreatitis | 1,080 | | N.T. | | 2·969 | <0·01>0·001 | 1,754 | 2·002 | Not sig. | 27·6 | 1·538 | Not sig. |
| Chronic pancreatitis | | | | | | | | | | | | |
| Total | 284 | 4·577 | <0·001 | 307 | 5·059 | <0·001 | 549 | 5·352 | <0·001 | 9·5 | 4·745 | <0·001 |
| Normal vol. | 540 | 2·689 | <0·02>0·01 | 501 | 3·188 | <0·01>0·001 | 1,041 | 3·124 | <0·01>0·001 | 17·7 | 2·610 | <0·02>0·01 |
| Gall-bladder disease | 919 | 2·014 | Not sig. | 681 | 3·389 | <0·01>0·001 | 1,600 | 2·792 | <0·02>0·01 | 28·2 | 1·773 | Not sig. |

N.T. Significance not tested. Difference of means <3 S.E. of mean. *These values show a significant increase.
Not sig. P>0·05. Difference not significant.

cases have been calculated separately (Figs. 7 and 8). It was found that while the reduction of the bicarbonate output was just significant the total outputs of amylase and lipase were highly significantly reduced (Table III). The output of trypsin in the sample collected after pancreozymin (D4) was highly significantly reduced ($t = 3{\cdot}670$; $0{\cdot}01 > P > 0{\cdot}001$).

One of these patients with cancer involving the head of the pancreas showed a response with a volume of 336 ml. in 60 minutes (6·22 ml./kg. of body weight), 29·0 millimoles output of bicarbonate (0·54 m.mole/kg. of body weight) and enzyme outputs in excess of the normal mean. When this individual was excluded from the analysis, in the six remaining cases the reduction in bicarbonate output was highly significant ($t = 3{\cdot}024$; $0{\cdot}01 > P > 0{\cdot}001$), and the significance of the reduction of enzymes was increased.

CANCER OF THE BILIARY TRACT.—In four patients with cancer arising primarily in the bile ducts and obstructing the flow of bile, a normal pancreatic response to secretin and pancreozymin was obtained. Though the mean volume was slightly reduced due to bile duct obstruction, the mean bicarbonate concentration was high, and consequently the mean output of bicarbonate normal. The mean enzyme output was somewhat reduced.

PANCREATITIS.—The 29 cases of pancreatitis available for statistical study have been divided into groups, one "post-acute pancreatitis", the other chronic pancreatitis. In the "post-acute" group were included (*a*) those who had suffered from acute pancreatitis and were studied during the attack or up to nine months after recovery and (*b*) those who had had recurring attacks of pancreatitis but showed no evidence of permanent pancreatic damage such as continuing diabetes, steatorrhoea, or calcification of the pancreas, and when followed for a period had remained well, in some instances after surgery of the biliary tract. The chronic pancreatitis group included those patients presenting with long-standing attacks, with evidence of permanent glandular damage such as diabetes, steatorrhoea, or calcification, and those in whom the surgeon noted a sufficient hardening in the gland to justify without doubt such a diagnosis. Such a division, though arbitrary, appears to be a valid functional classification.

"*Post-acute Pancreatitis.*"—Associated gall bladder disease was found in eight of the 14 patients in this group. The mean results of the whole group show no significant deviation from normal apart from an increased volume in the post-secretin period. In one patient the concentration and output of enzymes was markedly reduced in spite of a normal volume and bicarbonate. In another patient who was inadvertently intubated during a mild attack of acute pancreatitis a raised volume (6·46 ml./kg.) and high bicarbonate output were obtained (0·50 m.mole/kg.) but the output of enzymes was normal.

*Chronic Pancreatitis.*—In the 15 cases of chronic pancreatitis evidence of more marked functional impairment is found, the volume and bicarbonate being reduced (Tables I and II). Since the common bile duct remains patent in most cases, the reduction in mean volume is not so great as in the cancer group but the bicarbonate output is even lower in spite of the contribution made by the liver and gall bladder bile to the total bicarbonate (Fig. 6). The mean outputs of amylase, trypsin, and lipase all showed a significant reduction ($0{\cdot}01 > P > 0{\cdot}001$) in the post-secretin sample (D1) and a more marked reduction ($0{\cdot}001 > P$) in the post-pancreozymin sample (D4), and the total output of enzymes was also markedly reduced ($0{\cdot}001 > P$). A normal volume and enzyme response but elevated bicarbonate output was obtained in a patient in whom the chronic pancreatitis was localized to the head of the pancreas.

The individual total volumes fell within normal limits in seven of the 15 patients with chronic pancreatitis, and the mean output of bicarbonate and enzymes for this subgroup has been calculated separately (Fig. 7 and 8, Tables I and II). It was found that the mean output of bicarbonate was highly significantly reduced as were also the mean total outputs of amylase and lipase (Table III). The mean output of trypsin in the sample collected after pancreozymin D4 was significantly reduced ($t = 2{\cdot}348$; $0{\cdot}05 > P > 0{\cdot}02$).

Taking the cases of pancreatitis as a whole, it appears that normal function may be retained or rapidly regained after an attack of acute pancreatitis. Mild functional impairment may be demonstrated only by a poor enzyme output which is more obvious in post-pancreozymin values, and at a later stage bicarbonate output becomes affected and finally the volume reduced.

GALL BLADDER DISEASE.—This is a heterogeneous group of 27 patients who had non-malignant disease affecting the gall bladder or bile ducts. In 11 patients cholecystectomy had been done before the intubation, without relief of symptoms. The feature of the whole group was a statistically significant increase in the mean volume of the duodenal contents, expressed per kilogram of body weight (Tables I and III). There is no change in the output of bicarbonate though the maximum mean bicarbonate concentration in D3 specimen is reduced to

TABLE IV
NUMBER OF VALUES SIGNIFICANTLY DECREASED AND (IN BRACKETS) INCREASED IN INDIVIDUAL TESTS

| Diagnosis | No. of Cases | Volume | | Bicarbonate | | | Amylase | Trypsin | Lipase |
|---|---|---|---|---|---|---|---|---|---|
| | | D1–6 | D1–3 | Maximum | D1–6 | D1–3 | D4–6 | D4–6 | D4–6 |
| Cancer of pancreas | 17 | 10 | 11 | 12 | 11 (1) | 12 (1) | 15 | 13 | 13 |
| Pancreatitis: | | | | | | | | | |
| (*a*) Post-acute | 14 | 1 (3) | 1 (4) | 0 | 1 (3) | 0 (3) | 2 | 1 | 3 |
| (*b*) Chronic | 15 | 8 | 8 | 10 | 9 | 11 (1) | 9 | 7 | 8 |
| Gall-bladder disease | 26 | 2 (4) | 2 (3) | 2 | 5 (2) | 4 (2) | 1 | 4 (1) | 5 |
| Cancer of bile ducts | 4 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Non-pancreatic steatorrhoea | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Miscellaneous | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

8·8 m.mole%, a significant difference ( $t = 3{\cdot}235$; $0{\cdot}01 > P > 0{\cdot}001$). This increase in volume and lowered concentration of bicarbonate, present also in specimen D1 but most marked in specimen D3, is characteristic of gall bladder dysfunction and is due to the diluent effect of hepatic bile which the damaged gall bladder is unable to accept. There is some evidence of a reduction in the output of enzymes, particularly in the post-pancreozymin samples. In retrospect it seems likely that one if not two of the patients included in this group had impaired pancreatic function as well as primary biliary disease, but the exclusion of these cases does not substantially alter the mean results, or invalidate the conclusions drawn from them.

NON-PANCREATIC STEATORRHOEA.—The mean volume and mean output of bicarbonate and enzymes did not differ significantly from the normal means in five patients in whom the steatorrhoea was due to defective intestinal absorption.

MISCELLANEOUS GROUP.—Normal responses were obtained in two patients suffering from cirrhosis of the liver and in a third patient with essential hyperlipaemia.

### SIGNIFICANCE OF INDIVIDUAL TESTS

From the mean $\pm$ 2 standard deviations of the values obtained in the normal group the normal limits for individual tests have been determined. There was no advantage in adjusting the data in terms of body weight, since the coefficient of variation for the normal volume and bicarbonate output and output of enzymes was not reduced by this manoeuvre. The output of enzyme obtained in response to pancreozymin (samples D4-6) was chosen as the best index of enzymatic activity of the pancreas since the variability of these samples in the normal group was less than either the post-secretin period or total output of enzyme, and since a comparison of the means of this value in pancreatic disease and in normal subjects had shown the maximal difference statistically (Table III).

The number of occasions in which abnormal values were obtained in the various pathological groups is recorded in Table IV. The abnormal results were in most cases reductions, but occasionally, as shown in the table, values were found which exceeded the upper normal limit. An indication of the value of this test in individual cases is that abnormally reduced values were found in 15 of the 17 cases of carcinoma and 12 of the 15 cases of chronic pancreatitis. In nine of the 14 cases in these two groups in which the volume of duodenal contents was within normal limits the value for bicarbonate or one or more enzymes or for both bicarbonate and enzymes was significantly reduced.

### DISCUSSION

It is a measure of the success of the experiments of Ågren and Lagerlöf (1936) that their technique has been universally adopted with but few modifications. The method can be criticized in that duodenal intubation is irksome to an ill patient, difficult for the inexperienced technician to master, and necessitates readily accessible screening facilities. When duodenal intubation is practised occasionally or in ill patients, the gradual method of intubation is commended. Failure by this method is very rare and can be attributed to inadequate preparation of the patient by explanation, or to passing the tube too far in the early stages. Another fault which leads to failure to intubate the duodenum is the use of a tube which has been stored tightly curled.

When Crick *et al.* (1949) prepared samples of secretin and pancreozymin which were free from toxic and anaphylactic effects on animals an opportunity presented to examine the action of these preparations in man. The present experiments were designed primarily to elucidate the effect produced on the human pancreas by pancreozymin and further to determine the value of pancreozymin, a specific enzyme stimulant, in diagnosis. It seemed appropriate to test the effects of pancreozymin against a background of secretin-induced pancreatic secretion. The pattern of test designed by Ågren and Lagerlöf was therefore modified by injecting pancreozymin intravenously some 25 to 30

minutes after the infusion of secretin, at a time when the stimulant action of secretin on the flow of pancreatic juice, still apparent, ensured quantitative recovery of the duodenal contents, and after the washing out of preformed enzyme from the pancreatic ducts by secretin had been completed. This design of the experiments has permitted in addition a comparison of the actions of secretin and pancreozymin.

The methods used to measure pancreatic enzyme concentration in duodenal contents have been chosen with care. For amylase, Lagerlöf's modification of the method of Nørby (Lagerlöf, 1942) has been successfully employed, and tryptic activity has been assessed by the method devised by Gowenlock (1953) for this study, in which denatured human serum protein is the substrate and the phenolic substances liberated by trypsin are measured colorimetrically. The method, analagous to Hunt's (1948) method for the estimation of pepsin, obviates the difficulties encountered in titrimetric methods for trypsin such as that described by Lagerlöf (1942) where the high concentration of bile pigments in the duodenal samples obtained in response to pancreozymin obscured the titration end-point. The method of Cherry and Crandall (1932) has in our hands proved the most convenient for the estimation of lipase. In subjects with a normal pancreas the output of enzymes measured by these methods shows considerable parallelism (Fig. 4).

Although all three enzymes—amylase, trypsin, and lipase—have been estimated in these experiments, in practice only one need be investigated, and amylase is the enzyme of choice. In only one of the 32 cancer and chronic pancreatitis patients was the post-pancreozymin amylase normal in the presence of an abnormal trypsin or lipase. In the groups of cancer and chronic pancreatitis cases with normal duodenal volumes the mean reductions of amylase and lipase, expressed as percentages of the normal outputs, were about the same, but the mean reduction in trypsin was considerably less, although with the small number of cases involved this apparent "dissociation of enzymes" is not statistically significant. Lagerlöf (1939) also noted that trypsin activity in duodenal contents might be normal when the amylase output was depressed after acute pancreatitis, and somewhat similar results have been reported by Diamond and Siegel (1941).

Before accepting this indication of a dissociation of pancreatic enzymes in disease, it would be essential to prove that proteolytic activity of the duodenal contents is wholly due to pancreatic trypsin and not in part the result of proteolytic enzymes in intestinal secretion, which would not be affected in pancreatic disease. On this point we have no evidence. The practical conclusion, however, is that in the diagnostic use of the secretin-pancreozymin test trypsin and lipase estimations may be omitted. This is of advantage not only in saving laboratory time but because these enzymes are more labile than amylase and require careful preservation during and after the period of collection by cooling in the presence of glycerol.

In normal man, following secretin, the volume of duodenal contents rises. A second rise in volume follows pancreozymin, largely if not entirely due to the presence of cholecystokinin in preparations of pancreozymin. So far as is known, cholecystokinetic activity usually accompanies pancreozymin activity on purification (Harper, 1959; Jorpes and Mutt, 1959) and there is only one report of the two having been separated (Greengard and Ivy, 1945). However, this permits a simultaneous assessment of gall bladder and pancreatic function in man when the secretin-pancreozymin test is used (Duncan *et al.*, 1952; Burton *et al.*, 1960a.

In pancreatic disease functional impairment of the gland has been most often demonstrated in patients with cancer of the pancreas and chronic pancreatitis. In cancer, where the obstructive element is the more marked, the characteristic feature in response to secretin is a reduced volume of the duodenal contents whereas in chronic pancreatitis where destructive features dominate, a reduced output of bicarbonate is more prominent. The post-secretin (D1-3) output of bicarbonate was significantly low in only one of the six patients with a normal post-secretin volume in the cancer group compared with three of seven such patients in the chronic pancreatitis group. This distinction between the two groups has been stressed by Dreiling (1951, 1953) and reaffirmed by Dreiling and Janowitz (1956), but too much importance should not be made of the distinction when assessing the pathology of an individual case since duct obstruction from inflammation and stones is sometimes found in chronic pancreatitis, and accompanying pancreatitis and atrophy are not uncommonly encountered in primary cancer of the pancreas. Hence in either disease a reduction of volume or of bicarbonate in response to secretin may predominate.

The consensus of opinion is that enzyme estimations add little to the diagnostic value in the secretin test (Dornberger *et al.*, 1948), and recently Sun and Shay (1957) omitted them when using the test. Parasympathomimetic agents such as mecholyl (Comfort and Osterberg, 1940) and insulin (Diamond and Siegel, 1940; Friedman and Snape, 1950), which have been used in conjunction with

secretin to stimulate enzyme production, have the disadvantage of producing many side effects. It was therefore of particular interest to determine whether by the addition of the specific enzyme stimulant pancreozymin alterations in enzyme output in pancreatic disease could be detected, which were not apparent in the response to secretin alone. The significance of the differences between the mean outputs of enzymes in the normal group and in the groups of patients with chronic pancreatitis and cancer of the pancreas, in whom the volume of duodenal contents was normal, was tested statistically. The outputs after secretin (D1-3) and after pancreozymin (D4-6) were examined separately, and for all three enzymes the "t" values were greater after pancreozymin than after secretin. This result, which follows from the greater scatter of individual results in the immediate post-secretin (D1) sample than in the post-pancreozymin (D4) sample, should make abnormalities in enzyme output more easily detectable in the post-pancreozymin period. This is so in fact, and we have found in cancer of the pancreas that diminution in post-pancreozymin output of enzyme is a more sensitive index of impaired pancreatic function than lowered volume of bicarbonate.

Dreiling and Hollander (1950) found that the scatter of enzyme results after secretin was reduced if the results were related to body weight, and suggested that in earlier investigations a variable contamination of secretin by pancreozymin might have been one factor in producing the scatter. The secretin used in our experiments was free of pancreozymin, and there was no reduction in scatter when the results were expressed in terms of body weight. Marks and Tompsett (1958) have reported observations in which pancreozymin was given 60 minutes after secretin, but they pooled all their samples and estimated an 80-minute amylase concentration. In our experiments this corresponds most closely to the total (D1-6) amylase output which we have found a less sensitive index of abnormality than the post-pancreozymin (D4-6) output.

When the individual results in the cancer of the pancreas and chronic pancreatic groups are considered, and the enzyme response to pancreozymin compared with the bicarbonate response to secretin a difference between the cancer group and chronic pancreatitis group emerges. The post-pancreozymin (D4-6) output of amylase was significantly decreased in 15 of the 17 patients in the cancer group, whereas the post-secretin (D1-3) output of bicarbonate was low in 12. The post-pancreozymin output of amylase was low in only nine of the 15 patients in the group with chronic pancreatitis whereas the post-secretin output of bicarbonate was reduced in 11 patients (Table IV). From this the output of enzyme in response to pancreozymin appears to be more valuable in the diagnosis of cancer of the pancreas than of chronic pancreatitis. The serum enzymes evoked in response to secretin and pancreozymin were significantly elevated in one of the two cancer cases and four of the six cases of chronic pancreatitis in which the post-pancreozymin duodenal amylase was normal. A combined study of duodenal contents and serum enzymes, as suggested by Sun and Shay (1957), does therefore lead to a high proportion of significantly positive tests, 29 out of 32, in these two groups.

After acute pancreatitis evidence of impaired pancreatic function is not often met since severely ill patients are not tested and in milder attacks rapid restoration of function ensues. As Dreiling (1953) has indicated, use may be made of this as a prognostic test. If pancreatic function is impaired more permanent structural damage associated with chronic pancreatitis is likely to persist after an acute attack. Since this may lead to further attacks the test can be used to indicate the necessity for further definitive treatment.

In gall bladder disease a significant rise in the volume of duodenal output following secretin has been recognized (Ågren and Lagerlöf, 1937). This increase, due to the increased flow of hepatic bile when gall bladder function is impaired, we have found to be associated with a mean decrease in concentration of bicarbonate in post-secretin samples (D1 and D3) though the output of bicarbonate in these samples is normal. Concentration values of bicarbonate should not therefore be used to indicate pancreatic dysfunction in the presence of gall bladder disease. The few instances of lowered post-pancreozymin enzyme found in gall bladder disease have been attributed to unrecognized pancreatitis.

The secretin-pancreozymin test can distinguish in obstructive jaundice between primary cancer of the bile ducts (in which pancreatic function is normal) and primary cancer of the pancreas. Again it can with certainty distinguish between steatorrhoea associated with pancreatic insufficiency and non-pancreatic steatorrhoea. The presence of blood in duodenal samples has indicated involvement of the duodenum by growth.

Though pancreatic disease is manifest when diminished volume and output of bicarbonate and enzymes are present, mention must be made of certain elevated values which have been encountered. In four of the five patients tested within 14 days of an acute attack of pancreatitis elevated values for post-secretin output of bicarbonate or output/kg.

of body weight were recorded. The post-secretin volume of duodenal contents was raised in three of these patients, in two of whom gall stones were present, but in the third gall bladder function was normal at the time of the test. A raised bicarbonate output was encountered also in two patients with gall bladder disease (one of whom had associated cholangitis), in a patient, already recorded, with an early cancer of the head of the pancreas who had a raised output of pancreatic juice but normal gall bladder function, and in another with chronic pancreatitis localized to the head of the pancreas. It is difficult to attribute this finding to gall bladder disease solely since gall bladder function was normal in at least three of these patients, and it can only be assumed that at an early state of pancreatic injury an increased flow of pancreatic juice with normal bicarbonate concentration (but high bicarbonate output) may result from stimulation with secretin. The post-pancreozymin output of enzymes was not increased in any of these cases. A similar abnormal secretory response was reported by Gross, Comfort, Wollaeger, and Power (1950) in parenchymatous hepatic disease. Liver damage, however, cannot explain the findings in our cases. Lake (1947) and Andrus, Lord, and Lake (1942) have reported a patient with cancer of the pancreas with functional overactivity of the pancreas. None of these patients had severe attacks of pancreatitis and the possibility remains that in mild pancreatitis the pancreas may excrete excessive fluid of normal bicarbonate concentration in response to secretin in the acute and early recovery phase.

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# SERUM AMYLASE AND SERUM LIPASE LEVELS IN MAN AFTER ADMINISTRATION OF SECRETIN AND PANCREOZYMIN

BY

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A simple evocative test has been used to study pancreatic function. Serial estimations of amylase and lipase in blood serum are made at intervals up to six hours and again at 24 hours after injecting intravenously standard doses of secretin and pancreozymin. The results of 213 tests on a normal group, in pancreatic disease, in biliary and hepatic diseases have been analysed and compared with the results of duodenal intubation and an oral glucose tolerance test. A combined evocative test and oral glucose tolerance test provide evidence of pancreatic dysfunction in the majority of cases of cancer of the pancreas and chronic pancreatitis. The conditions of the test are described and the pathological lesions in which false positive evocative tests may be found are indicated.

The simple evocative test provides the earliest biochemical evidence of pancreatic disease in some patients with cancer of the pancreas and chronic pancreatitis.

Though part of the amylase found in the blood stream of man in health may derive from the liver and salivary glands, most of it originates in the pancreas. There is little lipase of pancreatic origin in the blood of normal man, though serum contains esterases which are capable of acting on esters of fatty acids of low molecular weight. In pancreatic disease, however, pancreatic duct obstruction may lead to the passage of amylase and lipase from the acini and ductules of the pancreas into the portal blood stream and increased amounts of enzymes are found in systemic venous blood. In clinical practice estimation of serum amylase and lipase has proved of great value in diagnosing an acute attack of pancreatitis, although in chronic pancreatitis and cancer of the pancreas even repeated estimations of the enzymes are less helpful. This can be attributed to a more gradual obstruction of the duct and a diminution *pari passu* in functional activity of the gland in these diseases.

Many workers have tried to modify the conditions in which serum enzymes are measured in order to increase the sensitivity of the tests in chronic and relapsing pancreatitis and in cancer of the pancreas. This has been done in three ways; by stimulating the gland to secrete in response to secretin and parasympathomimetic drugs, by giving morphine to induce spasm of the sphincter of Oddi and thus increase pressure in the ducts, or by combining these methods.

Popper and Necheles (1943) showed experimentally in dogs that if the pancreas was powerfully stimulated by a combination of secretin and mecholyl the serum lipase rose in animals with a normal pancreas but not in those in which the pancreas had atrophied. By contrast a less vigorous stimulus, secretin alone, produced no elevation in normal dogs, but a rise was found after the pancreatic duct was tied (Popper, Olson, and Necheles, 1943). Since then evocative serum enzyme studies have developed clinically along the two main lines which correspond with these experimental findings. It is necessary to draw a clear distinction between the two which are frequently confused. The first type of test is designed, by intense stimulation (frequently combined with morphine), to produce in subjects with a normal pancreas a rise in serum enzyme levels, which would be less marked or absent in chronic destructive lesions of the gland. In the second type a milder stimulus is applied which would not raise the serum enzyme levels appreciably if the outflow from the healthy gland was unobstructed, but might be expected to do so if the glandular secretion were dammed up behind an

inflammatory or malignant obstruction of the duct.

As an example of the first variety, which might be called a combined obstructive-evocative test, Myhre, Nesbitt, and Hurly (1949) made serial determinations of serum enzymes after vigorous stimulation of the pancreas with secretin and the parasympathomimetic drug mecholyl, with the addition of morphine. They obtained no elevation of serum amylase and lipase in patients with advanced pancreatic disease. However, a significant rise of serum enzymes was found in only 70% of normal subjects, a proportion not sufficiently high to justify the use of their secretin-mecholyl and secretin-morphine tests in clinical practice. For this reason the method has been largely discarded.

The alternative method, a simple evocative test in which a milder stimulus is given, proved more promising. Prostigmin methyl sulphate intramuscularly (Knight, Muether, and Sommer, 1949) and secretin intravenously (Lopusniak and Bockus, 1950) were given to normal subjects and patients with pancreatic disease. In the normal group no elevation of serum enzymes was observed, but in some cases of pancreatitis and cancer of the pancreas a rise occurred. Lopusniak and Bockus found that this rise was more likely to occur when the initial enzyme values were high but was less often seen in patients with normal resting values. Dreiling and Richman (1954) reviewed the literature and concluded that evocative serum enzyme studies of this type after intravenous secretin were less useful than other methods of evaluating pancreatic function, such as the study of secretin-stimulated pancreatic secretion. In their own experiments, however, Dreiling and Richman did not estimate serum lipase but relied solely on serum amylase values.

While carrying out a study of the effect of secretin and pancreozymin on the amount and composition of duodenal contents (Burton, Evans, Harper, Howat, Scott, Oleesky and Varley, 1960), we have also made serial observations on the levels of serum amylase and lipase before and after stimulating the pancreas. An analysis of the results has been made and correlated with the state of pancreatic function determined by examining duodenal contents and by performing a standard oral glucose tolerance test.

## Methods

Secretin and pancreozymin were prepared from pig intestine and assayed according to the method of Crick, Harper, and Raper (1949). Tests of toxicity and for anaphylaxis were carried out. Details of the preparation and administration of the extracts are given elsewhere (Burton *et al.*, 1960). In most instances the dose of both secretin and pancreozymin has been 1·7 units per kilogram of body weight.

The patient fasts overnight. A control sample of about 10 ml. of venous blood is collected, after which secretin is given intravenously. Twenty-five minutes later a post-secretin sample is removed, after which the appropriate dose of pancreozymin is injected. Thirty minutes later a post-pancreozymin sample is collected. Further blood samples are taken, two, four, and six hours after secretin. Food is permitted after the two-hour sample, and in most cases a postprandial sample has been collected 24 hours later.

Serum amylase is estimated by a modification of the saccharogenic method of Somogyi (1938), reducing substance being measured by Maclean's method and serum lipase by a modification of the method of Cherry and Crandall (1932) in which triolein is the substrate. Attempts made in our laboratory to estimate changes of esterase in the serum of patients with pancreatic disease, using tributyrin as substrate, according to the method of Goldstein and Roe (1943) and Goldstein, Epstein, and Roe (1948), have proved unsuccessful. Henry, Sobel, and Berkman (1957) report a similar failure in acute pancreatitis in man. The Somogyi and Cherry and Crandall techniques have given results which are easily reproduced with accuracy. In duplicate analyses of amylase on 27 specimens of serum, in which the values ranged from 19 to 332 units per 100 ml., the range of the differences between duplicate analyses was 0 to 28 units per 100 ml., and the mean of these differences was 6·5 units per 100 ml. Duplicate analyses of lipase were made on 65 samples of serum and duodenal contents, with values ranging between 0·1 and 5·9 units per ml. The range of the differences between duplicates was 0 to 0·8 units per ml., and the mean of these differences was 0·18 units per ml.

An oral glucose tolerance test of 50 g. of glucose has been given. Adequate carbohydrate intake has, as far as possible, been assured before the test has been accepted as valid. As it is convenient to express the results of the oral glucose tolerance test by a single figure, it has been assumed in this paper that glucose tolerance is impaired when the blood level of reducing substances exceeds 140 mg. per 100 ml. of capillary blood two-and-a-half hours after the oral dose of 50 g. of glucose has been given to a fasting patient and normal when the two-and-a-half hour value is less than this figure.

In many instances the duodenal juice has been quantitatively aspirated in the first hour after stimulation with secretin, and the volume, bicarbonate, and output of amylase, trypsin, and lipase obtained in response to pancreozymin have been compared with the response to secretin (*loc. cit.*).

## Results

Normal Subjects.—In a group of 51 normal individuals the mean fasting serum amylase was 70 units/100 ml. of serum (S.E. of mean $\pm$ 3·6). The upper limit of normal at the 99% limit of confidence (mean + 2·58$\sigma$) was 134 units. In 42 fasting normal persons the mean serum lipase was 0·51 $\pm$ 0·04 units/ml. of serum, the upper limit of

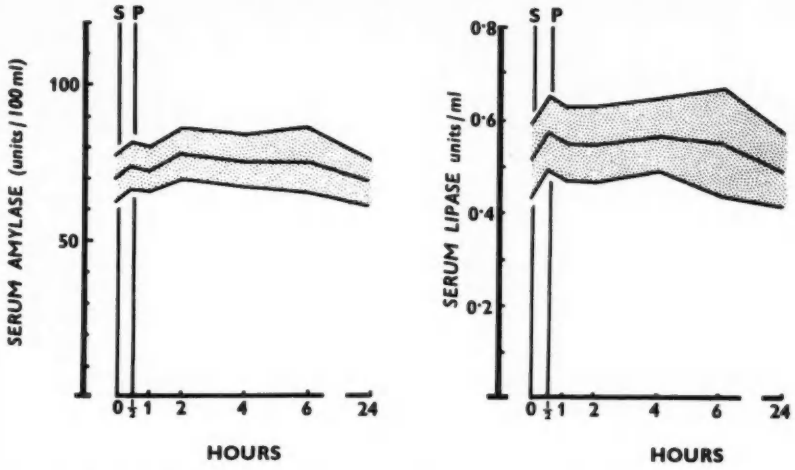



FIG. 1.—The Evocative Test.—*The pattern of the mean serum amylase in 51 normal subjects and the mean serum lipase in 42 normal subjects ± 2 S.E. of means, obtained in response to secretin (S) and pancreozymin (P).*

normal at the 99% limit of confidence being 1·15 units.

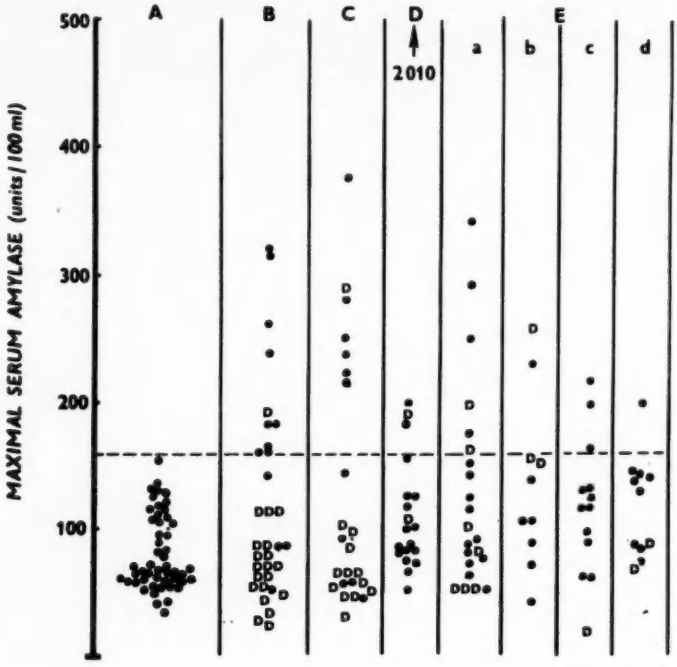
Serial enzyme estimations after secretin and pancreozymin were made in a normal group comprising 51 individuals, made up of (*a*) 26 healthy men and women aged 20 to 45 years in whom the pancreas was assumed to be normal, (*b*) 14 adult patients varying in age from 20 to 63 suffering from various diseases not affecting the liver, gall bladder, pancreas, or kidneys, and (*c*) 11 adult patients aged 45 to 75 suffering from malignant disease not involving the extrahepatic bile ducts or pancreas.

For the individual in health both serum amylase and serum lipase are relatively constant over a period of time. The mean of the differences between the fasting control sample and the postprandial sample taken 24 hours later in the normal group was for amylase 12·5 units (43 subjects) and for lipase 0·12 units (38 subjects).

The pattern of the mean response of serum amylase and lipase to secretin and pancreozymin in the normal group is shown in Fig. 1. There is no significant difference in either serum amylase or lipase between any of the three subgroups which have been combined to form the normal group for serum enzymes. In the 51 subjects of this normal group in whom serum amylase was measured there is no significant alteration in the enzyme levels in the first three samples. The slightly higher means for the fourth and fifth samples are derived from a smaller number of observations (44 and 41 respectively) than those for the first three samples. By chance the cases unrepresented in the fourth and fifth means had rather low serum enzyme levels which explains the fortuitous increase in these means. No significant pattern can be discerned in the mean values in the 42 subjects in whom serum lipase was recorded. It seems reasonable to derive from the highest enzyme value reached in each subject a measure of the upper limit of serum amylase and lipase in normal subjects after secretin and pancreozymin (Fig. 2). In the normal group the mean maximal concentration of amylase was 83 ± 4 units/100 ml. and of lipase 0·7 ± 0·05 units/ml. At the 99% limit of confidence the normal maximal amylase was 158 units/100 ml. of serum and the maximal lipase 1·5 units/ml. of serum. In 21 of the 40 cases of the first two subgroups of the normal group the duodenal contents have been recovered. This modification of the test was not found to alter the pattern or values of the responses. In the normal group the postprandial values for both serum amylase and lipase taken 24 hours later all fell within the normal range of values.

PANCREATIC DISEASE.—Results are expressed in terms of (1) cancer of the pancreas and (2) pancreatitis.

(1) *Cancer of the Pancreas.*—Primary cancer of pancreas was studied in 36 patients, the location of all but one being verified at operation or at necropsy. Three of these were studied following subtotal



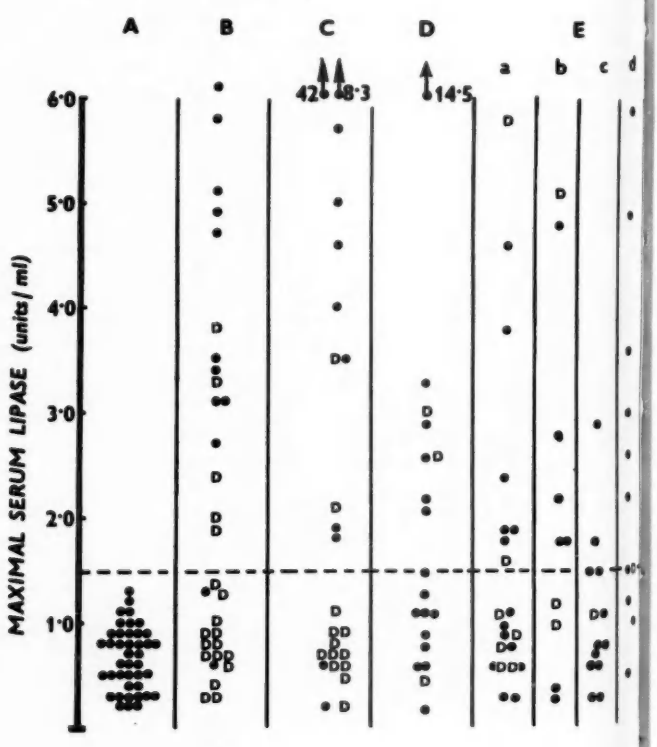




FIG. 2.—The Evocative Test.—*The distribution of the maximal serum amylase and lipase evoked by secretin and pancreozymin in normal and abnormal subjects* (•- *non-diabetic;* D,-*diabetic*). *The upper limits of normal* (*for amylase 158 units/100 ml. and for lipase 1·5 units/ml.*) *are indicated by interrupted lines.*

*A. Normal group*
*B. Cancer of pancreas*
*C. Chronic pancreatitis*
*D. "Post-acute pancreatitis"*
*E. Biliary disease*
(a) *of gall bladder*
(b) *of common bile duct*
(c) *post cholecystectomy*
(d) *cancer of the biliary tract*

pancreatectomy. Of the remaining 33, 16 originated in the head of the pancreas, 10 in the body, three occupied both regions diffusely, and four were ampullary cancers. At operation carried out at about the time of the test secondary deposits were obvious in the liver in nine of the group. In two cases of primary cancer of the stomach the pancreas was secondarily involved.

Early in the study it was appreciated that a positive evocative response was less likely to be obtained in patients in whom hyperglycaemia and glycosuria had been found. Thereafter an oral glucose tolerance test was performed as near to the time of the evocative test as practicable and on the results 31 cases have been divided into 11 in whom the glucose tolerance test was negative (non-diabetic) and 20 in whom it was positive (diabetic). Collections of duodenal contents were made simultaneously with the evocative tests in 17 cases, and on these results two further subgroups have been distinguished. In 10 patients the volume of duodenal contents was significantly reduced (less than 150 ml. in 60 minutes). In seven of these the glucose tolerance was also impaired; in two it was normal, and in the tenth it could not be determined. In the seven patients with normal duodenal output, two had moderately and two slightly impaired glucose tolerance. The glucose tolerance was normal in the other three.

The mean responses of the 33 patients suffering from primary cancer of the pancreas and of the subgroups based on the results of the glucose

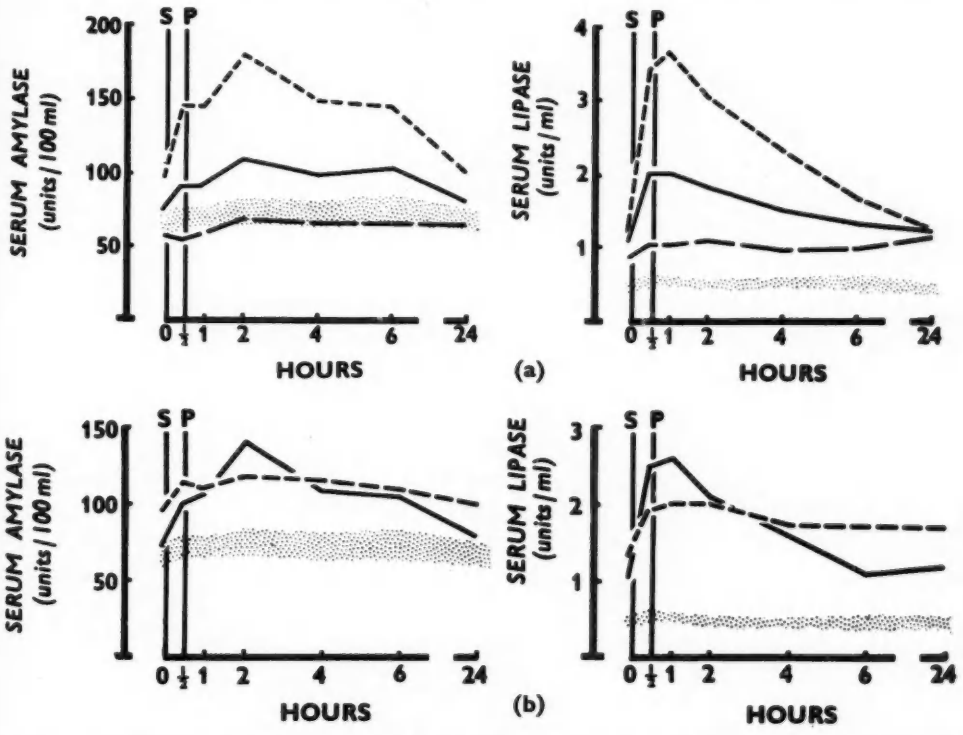



FIG. 3.—The Evocative Test.—*Mean serum amylase and lipase evoked by secretin (S) and pancreozymin (P) in cancer of the pancreas. The limits of normal (±2 S.E. of the normal means) are indicated by the stippled areas, while the figures in brackets indicate the number in each subgroup. The same symbols and conventions are used in Figs. 4 and 5.*

(a) *Whole group with diabetic and non-diabetic subgroups.*
——— *Whole group (33)* - - - - - - - - - - *Non-diabetic (11)* ——— ——— ——— *Diabetic (20)*

(b) *Subgroups with normal and reduced volume of duodenal contents.*
——— *Normal volume (7)* - - - - - - - - - - *Reduced volume (10)*

TABLE I

| Group | No. of Cases | Samples | | | | | | | Significance of Difference between Means | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Control Samples of Normal and Abnormal Groups | | | Sample in Abnormal Group Showing Maximum Increase (or Reduction) and Corresponding Normal Sample | | |
| | | Control | Post-SN | Post-PZN | 2 Hr. | 4 Hr. | 6 Hr. | 24 Hr. | t or c | P | Significance | t or c | P | Significance |
| | | AMYLASE | | | | | | | | | | | | |
| Normal<br>Standard error | 51 | 70<br>3·6 | 74<br>3·8 | 73<br>3·9 | 78<br>4·1 | 76<br>4·3 | 76<br>5·4 | 69<br>3·7 | | | | | | |
| Carcinoma of pancreas | | | | | | | | | | | | | | |
| Total | 33 | 75 | 90 | 92 | **108** | 97 | 102 | 81 | | | NT | 2·08 | <0·04>0·03 | + |
| GTT − ve | 11 | **98** | 145 | 145 | **180** | 149 | 145 | 100 | 2·54 | <0·02>0·01 | + | 6·80 | <0·001 | ++ |
| GTT + ve | 20 | **56** | 53 | 57 | 68 | 66 | 65 | 66 | 1·68 | <0·1>0·05 | 0 | 2·68 | <0·01>0·001 | ++ |
| Normal duodenal vol. | 7 | 72 | 99 | 105 | **141** | 108 | 103 | 78 | | | NT | 4·00 | <0·001 | ++ |
| Reduced duodenal vol. | 10 | **92** | 113 | 108 | **118** | 114 | 108 | 100 | 1·60 | <0·2>0·1 | 0 | 2·16 | <0·05>0·02 | + |
| Chronic pancreatitis | | | | | | | | | | | | | | |
| Total | 23 | 78 | 94 | 102 | **106** | 97 | 95 | 87 | | | NT | 1·59 | <0·2>0·1 | 0 |
| GTT − ve | 10 | **93** | 125 | 144 | **157** | 130 | 134 | 110 | 2·35 | <0·05>0·02 | + | 5·23 | <0·001 | +++ |
| GTT + ve | 13 | 66 | 71 | 70 | 71 | 72 | 62 | 68 | | | NT | | | NT |
| Normal duodenal vol. | 7 | 73 | 87 | 95 | **116** | 87 | 94 | 81 | | | NT | 2·24 | <0·05>0·02 | + |
| Reduced duodenal vol. | 7 | 65 | 59 | 61 | **57** | 61 | 62 | 64 | | | NT | 1·94 | <0·1>0·05 | 0 |
| Acute pancreatitis | 19 | **87** | 98 | 99 | **105** | 105 | 105 | 99 | 1·44 | <0·2>0·1 | 0 | 3·01 | <0·01>0·001 | ++ |
| Biliary tract and liver disease | | | | | | | | | | | | | | |
| Non-malignant group | | | | | | | | | | | | | <0·02>0·01 | |
| A. Gall-bladder disease | 22 | **89** | 109 | **111** | 110 | 97 | 97 | 81 | 1·58 | <0·2>0·1 | 0 | 2·49 | <0·001 | + |
| B. Duct lesions | 10 | 78 | 105 | 118 | 124 | 135 | **142** | 86 | | | NT | 3·82 | <0·02>0·01 | +++ |
| C. Cholecystectomy | 13 | 78 | 96 | 102 | **106** | 107 | 101 | 93 | | | NT | 2·64 | <0·05>0·02 | + |
| Carcinoma of biliary tract | 11 | 66 | 90 | 89 | **100** | 83 | 92 | 70 | | | NT | 2·27 | <0·2>0·1 | + |
| Liver group | 13 | 74 | 90 | **102** | 93 | 92 | 93 | 88 | | | NT | 1·51 | | 0 |
| | | LIPASE | | | | | | | | | | | | |
| Normal<br>Standard error | 42 | 0·5<br>0·04 | 0·6<br>0·04 | 0·55<br>0·04 | 0·55<br>0·04 | 0·6<br>0·04 | 0·55<br>0·06 | 0·5<br>0·04 | | | | | | |
| Carcinoma of pancreas | | | | | | | | | | | | | | |
| Total | 31 | **1·1** | **2·0** | **2·0** | 1·8 | 1·5 | 1·3 | 1·2 | 3·43 | <0·001 | +++ | 4·37 | <0·0001 | +++ |
| GTT − ve | 11 | **1·2** | **3·4** | **3·65** | 3·1 | 2·3 | 1·6 | 1·2 | 4·66 | <0·001 | +++ | 11·80 | <0·001 | +++ |
| GTT + ve | 19 | **0·9** | **1·0** | **1·0** | **1·1** | **1·0** | **1·0** | **1·1** | 2·73 | <0·01>0·001 | ++ | 3·40 | <0·01>0·001 | ++ |
| Normal duodenal vol. | 7 | **1·0** | **2·5** | **2·6** | **2·1** | **1·6** | **1·1** | **1·2** | 3·52 | ≏0·001 | +++ | 7·41 | <0·001 | +++ |
| Reduced duodenal vol. | 9 | **1·3** | **1·9** | **2·0** | **2·0** | **1·7** | **1·7** | **1·7** | 4·35 | <0·001 | +++ | 4·61 | <0·001 | +++ |
| Chronic pancreatitis | | | | | | | | | | | | | | |
| Total | 23 | **0·8** | 1·7 | **2·0** | 1·7 | 1·5 | 1·1 | 1·1 | 1·80 | <0·1>0·05 | 0 | 2·41 | <0·02>0·01 | + |
| GTT − ve | 10 | **1·1** | 2·95 | **3·7** | 2·9 | 2·4 | 1·6 | 1·6 | 3·86 | <0·001 | +++ | 7·83 | <0·001 | +++ |
| GTT + ve | 13 | 0·6 | 0·8 | 0·8 | **0·85** | 0·8 | 0·7 | 0·6 | | | NT | 1·73 | <0·1>0·05 | 0 |
| Normal duodenal vol. | 7 | **0·8** | 2·0 | **2·3** | 1·8 | 1·6 | 1·05 | 1·0 | 2·34 | <0·05>0·02 | + | 5·10 | <0·001 | +++ |
| Reduced duodenal vol. | 7 | 0·5 | 0·4 | 0·4 | 0·5 | 0·5 | 0·4 | 0·5 | | | NT | | | NT |
| Acute pancreatitis | 18 | **1·0** | 1·25 | 1·2 | **1·3** | 1·3 | 1·15 | 1·0 | 3·79 | <0·001 | +++ | 5·46 | <0·001 | +++ |
| Biliary tract and liver disease | | | | | | | | | | | | | | |
| Non-malignant group | | | | | | | | | | | | | | |
| A. Gall-bladder disease | 21 | **0·7** | **1·3** | 1·2 | 1·3 | 1·2 | 0·7 | 0·5 | 1·30 | <0·2>0·1 | 0 | 2·39 | <0·02>0·01 | + |
| B. Duct lesions | 10 | **1·0** | **2·1** | 1·9 | 1·6 | 1·4 | 1·3 | 0·9 | 3·175 | <0·01>0·001 | ++ | 5·67 | <0·001 | +++ |
| C. Cholecystectomy | 13 | 0·55 | 1·0 | **1·0** | 0·9 | 0·7 | 0·9 | 0·6 | | | NT | 3·655 | <0·001 | +++ |
| Carcinoma of biliary tract | 11 | 0·6 | **2·4** | 2·1 | 1·8 | 1·4 | 1·15 | 0·7 | | | NT | 6·72 | <0·001 | +++ |
| Liver group | 11 | 0·7 | **1·4** | 1·35 | 1·2 | 1·0 | 1·0 | 0·9 | 2·175 | <0·05>0·02 | + | 4·14 | <0·001 | +++ |

Groups. GTT − ve and GTT + ve; patients in whom glucose tolerance was respectively normal or impaired.
Samples. Post-SN and Post-PZN; samples collected respectively 25 minutes after giving secretin and 30 minutes after giving pancreozymin.
Significance. The probability (P) and significance (Sig.) were ascertained by calculating t (Fisher, 1934) if the degrees of freedom, n, = or <60, or c if n >60 (Geigy, 1956). Means tested are in bold type.

| | | |
|---|---|---|
| NT | Significance not tested if mean $< \pm$ 3 S.E. from normal mean. | |
| 0 | P >0·05. | Difference not significant |
| + | P <0·05> 0·01. | Difference significant |
| ++ | P<0·01>0·001. | Difference highly significant |
| +++ | P<0·001. | Difference very highly significant |

tolerance test and the volume of duodenal contents have been graphed in Fig. 3. The numerical values of the means of the various samples will be found in Table I, with the statistical significance of the difference between the means (*a*) of the control samples of the normal and the various abnormal groups, and (*b*) of the sample in an abnormal group which showed the maximum increase (or reduction) after stimulation and the corresponding normal sample.

A feature of the contour of the mean responses of the whole cancer group (as in subdivisions of the group in which significant rises were evoked) has been the early rise of lipase, notably as early as 25 minutes after secretin was given. The maximal value was attained in the first post-pancreozymin sample taken at the end of an hour and was followed by a fall. The amylase, however, had not reached its peak until two hours after secretin was given. The amylase and lipase results in the cancer groups differed not only in their contour when graphed against time, but also in the extent to which they varied from the results in the normal group. With one exception the mean amylase in the control samples collected before secretin administration was similar to that of the normal group. The exception was the subgroup of non-diabetic cancer patients in whom the control amylase was significantly raised. After stimulation, again with one exception, there was a considerable rise in the amylase levels. The highest peaks reached were 180 units in the non-diabetic group and 141 units in those whose duodenal contents were normal in volume. The differences between these means and the corresponding figure for the normal group (78 units) were very highly significant. The smaller increases to 118 units in the subgroup with reduced duodenal volume and to 108 units in the whole group were nevertheless statistically significant. The exception was the diabetic subgroup in which the amylase levels were low throughout the test, the reduction in the post-secretin sample being statistically significant.

By contrast the lipase levels in the control sample were very significantly increased in the whole group and all the subgroups. The greatest increases after stimulation were to 3·65 units in the non-diabetic group and 2·6 units in the cases with normal volume of duodenal contents, but the total group and the subgroup with reduced duodenal volume also showed a marked increase to a level of 2·0 units. All these increases were very highly significant statistically, and even the considerably smaller rise to 1·1 units in the diabetic group was highly significant.

Since from the results on the control group it was known that the upper normal limits for amylase and lipase in the control samples were 134 and 1·15 units respectively, and the maximal post-stimulation values 158 and 1·5 units respectively, it was possible to determine in individual cases whether the test was positive (abnormally high) either in the control or post-stimulation samples (Fig. 2). The total number of patients with cancer of the pancreas in whom the secretin pancreozymin evocative test was positive is given in Table II, together with the

TABLE II

NUMBER OF PATIENTS WITH SIGNIFICANT VALUES

| Group | Serum Amylase | | | Serum Lipase | | | No. of Positive Evocative Tests | Total No. of Patients |
|---|---|---|---|---|---|---|---|---|
| | Control | Post-stimulation | 24 hr. | Control | Post-stimulation | 24 hr. | | |
| *Cancer of Pancreas* | | | | | | | | |
| Total group | 4 | 9 | 4 | 10 | 15 | 12 | 16 | 33 |
| Impaired G.T.T. | 1 | 1 | 1 | 4 | 5 | 4 | 5 | 20 |
| Normal G.T.T. | 2 | 7 | 3 | 4 | 9 | 6 | 9 | 11 |
| Low vol. D.J. | 3 | 4 | 3 | 3 | 3 | 5 | 5 | 10 |
| Normal vol. D.J. | 0 | 3 | 0 | 3 | 4 | 4 | 4 | 7 |
| *Chronic Pancreatitis* | | | | | | | | |
| Total group | 2 | 7 | 5 | 4 | 11 | 8 | 11 | 24 |
| Impaired G.T.T. | 0 | 1 | 1 | 1 | 2 | 1 | 2 | 13 |
| Normal G.T.T. | 2 | 6 | 4 | 3 | 9 | 7 | 9 | 11 |
| Low vol. D.J. | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| Normal vol. D.J. | 0 | 1 | 1 | 1 | 4 | 3 | 4 | 7 |
| *Post-acute Pancreatitis* | | | | | | | | |
| Within 10 days | 4 | 4 | 4 | 4 | 3 | 3 | 4 | 5 |
| Later | 0 | 0 | 0 | 3 | 5 | 5 | 5 | 15 |
| *Biliary Tract Disease* | | | | | | | | |
| Gall-bladder disease | 3 | 6 | 2 | 2 | 8 | 0 | 9 | 22 |
| Bile duct lesions | 0 | 2 | 0 | 2 | 6 | 2 | 6 | 10 |
| Post-cholecystectomy | 0 | 2 | 2 | 1 | 2 | 0 | 3 | 13 |
| Biliary cancer | 0 | 1 | 0 | 1 | 6 | 0 | 6 | 11 |
| *Liver Disease* | 1 | 2 | 0 | 1 | 3 | 1 | 3 | 13 |

analysis for diabetic and non-diabetic patients. Of the 20 patients with impaired glucose tolerance the control amylase was significantly elevated in one and the lipase in four; after stimulation the maximal lipase was raised in five. If the results for both enzymes in the diabetic group are combined, the evocative test gave a significant rise in five of the 20 patients whereas the control value was significantly raised in four. On the other hand, in the 11 non-diabetic patients control values for amylase exceeded normal in two and for lipase in four instances. Following stimulation the maximal amylase was significantly raised in seven and lipase in nine of the 11 patients. If the results for both enzymes are combined a raised value was found in six patients before and in nine after stimulation. In one of the two negative tests the primary lesion may have originated in the common bile duct. In both diabetic and non-diabetic patients serum lipase seemed to be a more sensitive index of pancreatic disease than serum amylase. The glucose tolerance could not be measured in two patients. One of these showed a significant rise in amylase (serum lipase was not estimated) and in the other high amylase and lipase values obtained in the control specimen were maintained throughout the test.

The postprandial serum amylase taken at 24 hours was high in the same four individuals as the fasting control serum amylase. The 24-hour serum lipase was raised in 12 patients, in seven of whom the fasting control lipase was raised. In all but two post-stimulation values had been significantly increased. In three of the patients with elevated fasting lipases the 24-hour value was normal and two of these showed little rise on stimulation with secretin and pancreozymin.

Between individual responses there were wide differences which were unrelated to the duration of symptoms. This lack of correlation was to be expected in view of the variation in invasiveness and in the site of the cancer. Nevertheless in the three cases of ampullary cancer studied within the first month of jaundice (a time during which cancer of the ampulla might be expected to produce duct obstruction rather than acinar destruction), a prompt and decided elevation of both amylase and lipase was obtained in the two cases studied only a fortnight after the onset of jaundice, but in the third studied at one month a significant rise in lipase only was evoked. In a fourth patient with ampullary cancer studied six months after the appearance of jaundice no rise in either amylase or lipase could be detected. Three patients in whom the cancer had been removed by subtotal pancreatectomy showed low initial values which changed but little after stimulation with secretin and pancreozymin.

(2) *Pancreatitis.*—Forty-four patients had suffered from pancreatitis. Two main divisions of the group are analysed, one "post-acute pancreatitis" (20 cases) and the other chronic pancreatitis (24 cases). In "post-acute pancreatitis" are included those patients who had suffered previously from acute attacks of pancreatitis but who showed no evidence of permanent pancreatic damage such as continuing diabetes, steatorrhoea, or calcification of the pancreas. The chronic pancreatitis group included those presenting with a long history of repeated attacks and showing evidence of permanent glandular damage such as diabetes, steatorrhoea, or calcification, and those in whom the surgeon noted unequivocal hardening of the pancreas sufficient to justify without doubt such a diagnosis.

One patient in the chronic pancreatitis group, in whom a gross elevation of the serum enzymes occurred after stimulation, is considered separately. Of the remaining 23 patients the glucose tolerance was impaired in 13. In 14 patients the duodenal contents obtained in response to secretin and pancreozymin were aspirated, and in seven of these the volume of the contents was low (less than 150 ml. in 60 minutes). The glucose tolerance was impaired in five of seven of these patients, but in only two of the seven in whom the volume was normal.

In the chronic pancreatitis group the results are of a pattern remarkably similar to that of cancer of the pancreas. The mean responses for the total group and the groups subdivided according to the glucose tolerance test and volume of duodenal contents are graphed in Fig. 4. The numerical values and statistical results are given in Table I. The amylase control level was significantly increased only in the group with normal glucose tolerance. After stimulation the increase in this group, to 157 units, was very highly significant. The peak response, 116 units, in the group in which the volume of duodenal contents was normal, was also significant, but neither the smaller increases in the total group and in those with impaired glucose tolerance nor the slight decrease in the patients with reduced volume of duodenal contents differed significantly from the corresponding mean results in normal subjects.

The lipase results were in general similar, except for a greater elevation above the normal means. The control levels of the groups with normal duodenal volumes and normal glucose tolerance were significantly increased, very highly so in the latter case. After stimulation not only did these groups reach very highly significant maxima of 2·3 units and 3·7 units respectively, but the lipase in the total group, in which the amylase was not

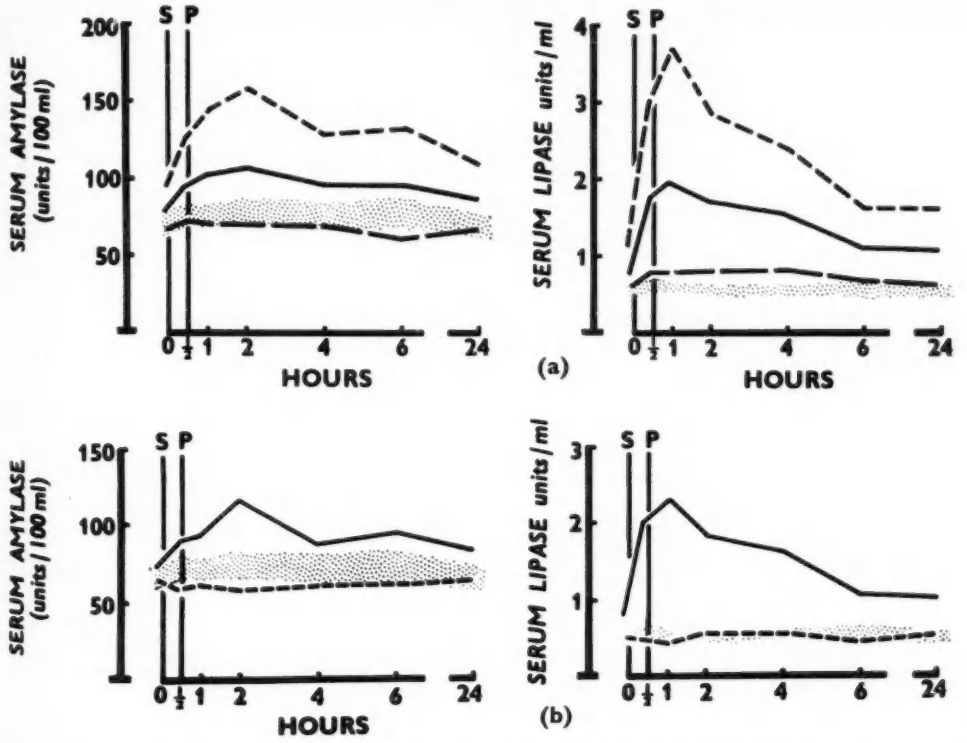



FIG. 4.—The Evocative Test.—*Mean serum amylase and lipase evoked by secretin and pancreozymin in chronic pancreatitis.*

(a) *Whole group with diabetic and non-diabetic subgroups.*
——————— *Whole group (23)* – – – – – – – – – – *Non-diabetic (10)* —— —— —— *Diabetic (13)*

(b) *Subgroups with normal and reduced volume of duodenal contents.*
——————— *Normal volume (7)* – – – – – – – – – – *Reduced volume (7)*

appreciably raised, was significantly increased to 1·7 units. In the more advanced cases, the groups with impaired glucose tolerance and reduced volume of duodenal contents, there was no significant difference from the normal group. In all the groups in which increases occurred in the mean serum enzyme, lipase attained its maximum earlier than the amylase.

As in the cancer cases, serum lipase seemed to be a more sensitive index than serum amylase in individual cases. A positive evocative test was more frequently obtained in the non-diabetic group than in the diabetic group (Table II). In none of the 13 patients with impaired glucose tolerance was the control serum amylase elevated; the control lipase was elevated in one. After stimulation the maximal amylase was significantly raised in one patient and the lipase in two. In the group of 10 patients with normal glucose tolerance the control amylase was raised in two and the lipase in two instances. Following stimulation a significantly increased value for amylase was attained in five cases and for lipase in eight. If the results for both enzymes are combined the evocative tests gave a significant rise in two of the 13 patients in the diabetic group whereas the control value was significant in one. In the non-diabetic group of 10 a significant rise was obtained in eight patients compared with a significant control value in three.

The postprandial serum amylase taken at 24 hours was high in four patients, in one of whom the fasting control value was raised; the postprandial serum

lipase was raised in seven patients, in three of whom the fasting control value was raised. In all seven well marked post-stimulation increases were obtained.

One patient with chronic relapsing pancreatitis and multiple stones in the pancreatic duct has been omitted from the analysis: in this instance the amylase rose from 80 to 379 units in six hours to reach 765 units at 24 hours and the lipase from 2·3 to 42 units at six hours, and fell to 21 units at 24 hours. Paradoxically the output of duodenal contents in 60 minutes was low (44 ml. in 60 min., 0·95 ml. per kilogram of body weight) though the glucose tolerance test was normal in this patient.

In the whole "post-acute pancreatitis group" the mean control serum amylase was not appreciably different from normal, but there was a highly significant maximal increase (to 105 units) after stimulation. The increase in both the control (1·0 units) and the maximal (1·3 units) lipase figures was very highly significant (Table I).

Five patients were examined within 10 days of an acute attack. One man was unwittingly stimulated during a mild attack of acute pancreatitis when the control serum amylase was 1,270 units and the control lipase 12·5 units. The maximal post-stimulation value for amylase rose to 2,010 units and lipase to 14·5 units. (This result is excluded from the calculation of mean values for the group.) In three of the other four patients examined within 10 days of the acute attack the control amylase was elevated, and the lipase in two of these three and one other. In all four one or other control value was abnormal. The post-stimulation serum amylase was significantly elevated in the same three patients as the control amylase and the post-stimulation lipase in two of the three in whom the control lipase was raised. A feature characteristic of the response of the immediate post-pancreatitis phase was that the post-stimulation values did not exceed the control values greatly; rather than a peak of response a plateau pattern was present.

Neither the control nor post-stimulation serum amylase was abnormal in any of the 15 patients examined after the tenth day following an attack, but the fasting serum lipase was abnormal in three of these patients and the post-stimulation serum lipase was elevated in these three and two others, five in all. The evocative test was positive in all three patients in whom the glucose tolerance test was impaired. The volume of the duodenal contents was not significantly reduced in any members of the group. In the whole group gall stones were present in four of the eight patients in whom the evocative tests were positive and in three of the 11 in whom they were negative.

BILIARY TRACT AND LIVER DISEASE.—A group of 69 patients with biliary tract and liver disease has been studied. It includes 45 patients with non-malignant disease of the gall bladder or bile ducts, 11 patients in whom cancer appeared to arise primarily in the gall bladder or bile ducts, and 13 patients with liver disease, two with acute hepatitis and 11 with cirrhosis of the liver.

(1) *Non-malignant Group.*—In 22 patients gall bladder disease with or without gall stones was present (gall bladder subgroup); 10 had lesions, either stone or simple stricture of the extrahepatic bile ducts (duct lesions subgroup); and in 13 the gall bladder had been surgically removed before the test (post-cholecystectomy subgroup). In all but three of this last subgroup lesions affecting the extrahepatic bile ducts were found at operation.

A number of diabetic patients known to have biliary disease was deliberately included in this study. A few patients included in this non-malignant group may possibly have suffered from pancreatitis, but unless there was either convincing evidence of this or the surgeon was able, at the time of operation, to demonstrate pancreatitis unequivocally the patient has been allocated to this group on account of the proved lesion of the biliary tract. Glucose tolerance was impaired in 11 of the 45 patients with simple biliary disease. The 11 cases were distributed as follows: seven in the gall bladder subgroup, three associated with lesions of the bile ducts, and one following cholecystectomy. The volume of duodenal contents aspirated in response to secretin and pancreozymin was not reduced in simple biliary tract disease.

The mean results in the three subgroups are shown graphically in Fig. 5. The numerical values and statistical evaluation are in Table I. The control lipase was significantly increased in the cases with duct lesions. Apart from this none of the pre-stimulation amylase or lipase values deviated significantly from normal. After stimulation, however, significant increases in amylase and lipase occurred in all three subgroups, the absolute increases and their statistical significance being greatest in the patients with duct lesions. Again in these groups the maximal elevation in lipase took place earlier than the maximal increase in amylase.

When the individual cases were considered (Table II), it was found that in the gall bladder subgroup the control amylase was elevated in three and the control lipase in two patients. A significant response for amylase was evoked after stimulation in six patients, and for lipase in eight, a combined response in nine of the 22 patients. At 24 hours the amylase remained elevated in two patients but the lipase was normal in all the cases in

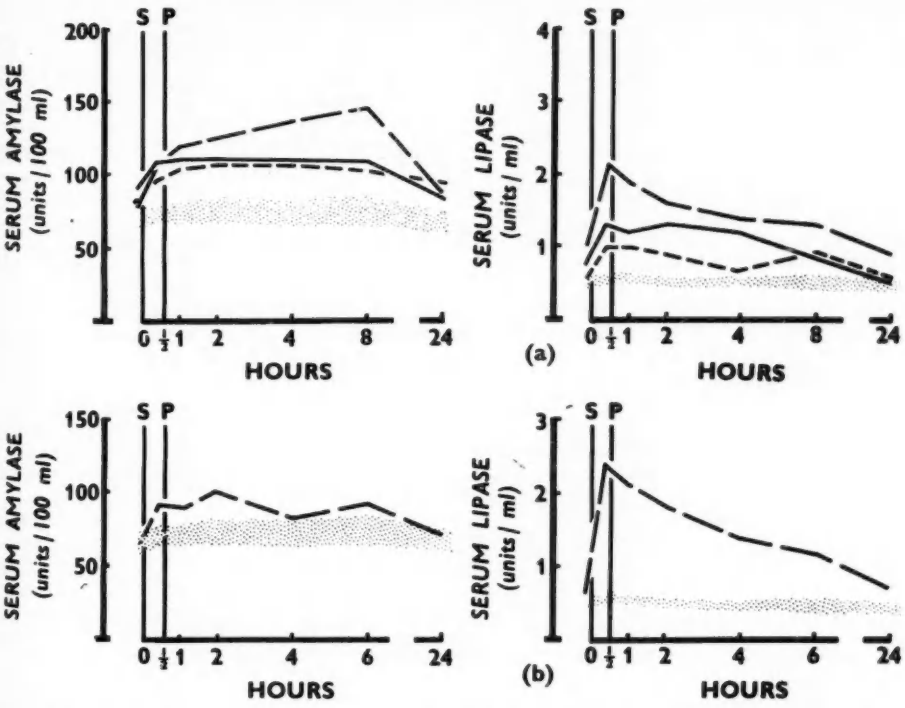



FIG. 5.—The Evocative Test.—*Mean serum amylase and lipase evoked by secretin and pancreozymin in biliary lesions.*

(a) *Non-malignant disease*
  (a) *of gall bladder* ———————— (*22*)
  (b) *of common bile duct* —— —— —— (*10*)
  (c) *post-cholecystectomy* - - - - - - - - - - - (*13*)
(b) *Cancer of biliary tract* (*11*).

which it was estimated. Three of the positive evocative tests were obtained in diabetic patients, in one of whom the rise of amylase from 103 to 200 units per 100 ml. and lipase from 0·8 to 5·8 units per ml. was striking. In the subgroup with duct lesions the control amylase was not elevated in any instance but the control lipase was abnormally high in two patients. After stimulation the maximal amylase became significant in two and the maximal lipase in six patients, a total of six of the 10 patients of the subgroup giving positive evocative tests. The 24-hour amylase was not elevated in any instance, but the 24-hour lipase remained elevated in the two patients with high control values. The test was positive in two of the three diabetic patients in this subgroup. In the post-cholecystectomy subgroup the control serum amylase was not raised in any individual, and the control serum lipase was high in one patient. After stimulation the serum amylase became significantly high in two patients and remained high in both at 24 hours. The serum lipase became high in two patients but had fallen at 24 hours. Of the 13 members of the subgroup the evocative test was positive in three, none of whom had an impaired glucose tolerance test.

(2) *Cancer of Gall Bladder or Bile Ducts.*—Primary cancer of the gall bladder was present in two and of the bile ducts in nine patients. The liver was grossly infiltrated with secondary deposits in two instances. Details of the mean results will be found in Fig. 5 and Table I. Before stimulation neither amylase nor lipase was increased. Two hours after secretin the mean amylase had increased significantly to 100 units. The lipase reached a very highly significant peak of 2·4 units in the sample collected 30 minutes after secretin. Examination

of the results in individual cases revealed that the control serum amylase was normal in all, but the control serum lipase was slightly raised (1·3 units) in one patient. After stimulation a significant response for amylase was obtained in one patient and for lipase in six patients including the one in whom the raised amylase had been found (Table II). The serum lipase attained its maximum 25 minutes after secretin in five of these tests, and one hour after secretin in the remaining positive test. The raised values for both amylase and lipase had all returned to normal in 24 hours. Neither of the two diabetic patients with biliary cancer had positive evocative tests. Gall stones were found at operation in four patients of the group, two of whom had positive evocative tests.

(3) *Liver Disease.*—Since serum lipase is sometimes elevated in cirrhosis of the liver, the test was performed on 13 patients, two with acute hepatitis and 11 with cirrhosis, none of whom had gall stones. There was no significant deviation from normal in the mean amylase results before or after stimulation in this group. In contrast the mean lipase was significantly raised before and very highly so after stimulation. Among the individual results one patient had a control serum amylase of 150 units which after stimulation rose 308 units. A positive amylase response was obtained in a second patient, but in neither was the 24-hour value raised. The control serum lipase was only slightly raised (1·2 units per ml.) in one of the group, but a rise was evoked in this patient and two other cirrhotic patients. The 24-hour value remained high (2·3 units per ml.) in the patient with the raised fasting control value. Of the 13 patients with liver disease a positive evocative test was present in three, all of whom had cirrhosis of the liver. Only one of four patients with abnormal oral glucose tolerance gave a positive evocative test.

Juxtapancreatic Disease.—Disease arising in organs and structures adjacent to the pancreas, other than in the biliary tract may involve the pancreas. Direct extension or pressure from such lesions was considered to be responsible for six positive evocative tests, in two cases of duodenal ulcer adherent to the pancreas, in two patients with cancer of the pylorus infiltrating the pancreas, and in two others in whom the cancer arose at a distance, in the bronchus and rectum respectively, but in whom the para-aortic lymph nodes of the posterior abdominal wall were grossly infiltrated. None of these patients was diabetic.

Miscellaneous Group.—A group was formed to include certain patients in whom the diagnosis remained in doubt. Negative evocative tests were obtained in two patients who had been suspected of having had acute pancreatitis, in a third patient whose abdominal pain resembled gall bladder or pancreatic pain, and in two diabetic patients the source of whose abdominal pain could not be traced.

It is convenient to include two other patients in this group who do not fall naturally into the classified groups, and both of whom gave positive evocative tests. A woman aged 67 years had received deep radiation therapy for a malignant ovarian tumour in 1952. In 1957 she developed acute upper abdominal pain followed by steatorrhoea, and a diagnosis of pancreatitis was made on clinical grounds. The serum amylase rose from a fasting value of 126 units to 177 units after stimulation and the serum lipase from 0·4 to 3·0 units. A man aged 58 had regional ileo-colitis densely adherent to the bladder and leading to chronic pyelonephritis and finally uraemia. The serum amylase rose from 115 to a maximum of 174 units per 100 ml., and the serum lipase from 1·5 to 2·4 units per ml. At necropsy three weeks later the pancreas was normal.

## Discussion

In 1954, Dreiling and Richman, summarizing the literature on evocative tests of pancreatic function to that time, comment that "the extensive investigations by many groups into serum pancreatic enzyme response to various secretagogues have produced such disparate findings and conclusions as to result in considerable confusion". Part of this confusion has been due to the failure of some workers to distinguish the two different conceptions underlying on the one hand the evocative-obstructive tests in which morphine is used in addition to pancreatic stimulants, and on the other the simple evocative tests in which no such agent is given to obstruct the pancreatic outflow.

The simple evocative test used in this study is based on the observation that an adequate but submaximal stimulation of the exocrine secretion of the pancreas will not lead to a rise in the pancreatic enzymes in blood serum when the gland is normal, but in the diseased gland, should the outflow of pancreatic juice be impeded, enzymes are absorbed into the blood stream after such stimulation and a significant rise in the amount of circulating pancreatic enzyme can be measured. This increase can of course occur only if the gland contains sufficient functioning acinar tissue to produce the enzymes.

So many different pancreatic stimulants have been used in such varied dosage in evocative tests that it

is not surprising that a consistent pattern of response has not emerged. Various parasympathomimetic drugs—mecholyl, carbachol, urecholine, and neostigmine—have been given to simulate vagal stimulation. But precise data on the influence of the abdominal vagus on the pancreas of man are not available and the effect of these drugs on the pancreas when used alone is unreliable (Thomas, 1950). The results are not necessarily reproducible since if the gastric contents are not removed a variable amount of gastric acid may pass into the duodenum to stimulate the pancreas secondarily through the physiological secretin and pancreozymin mechanisms. Secretin has also been used, some preparations of which have been free of enzyme stimulant, but others may have contained variable amounts of pancreozymin. Vagal stimulants have been given in conjunction with secretin to raise the concentration of enzymes in the pancreatic secretion.

Our investigations of the physiological activity of pancreozymin in man, planned to compare its action on duodenal contents with that of secretin, have provided a means of stimulating specifically the enzyme output of the pancreas. Secretin used in the dose of 1·7 units per kilogram of body weight and followed in half an hour by 1·7 units of pancreozymin has given results which in normal subjects fulfil the primary criterion of a simple evocative test of the pancreas, that in the normal pancreas a minimal and insignificant rise in serum enzyme values occurs. Unfortunately it is not possible to compare the results of our experiments with the effects of secretin alone on the serum enzymes, since this effect of secretin may not have been completed by the time pancreozymin is given 30 minutes later, and it was not considered justifiable to submit outpatients to a further test and series of venepunctures to decide this point. From the available data, however, it can be stated that in an appreciable number of the positive tests in abnormal subjects a prompt increase in enzyme, notably lipase, is present within 25 minutes of giving secretin in the blood specimen taken immediately before the pancreozymin is injected.

Before the investigation had been long in progress it was appreciated that the method of Goldstein and Roe we had adopted to measure serum lipase, though adequate for estimating lipolytic activity in duodenal contents, did not in fact measure the changes in serum lipase in response to pancreatic disease in man. Thereafter we used a modification of the method of Cherry and Crandall with olive oil as substrate, which gave good results in the hands of Lopusniak and Bockus (1950). Statistical comparison of the mean serum lipase obtained by this method with the mean serum amylase has proved that lipase in serum is a more sensitive index of pancreatic disease in both fasting control specimens and in evocative tests, a point not appreciated by workers who have used serum amylase alone to measure the effects of stimulation. From a scrutiny of our results this does not seem to depend on the amount of bilirubin in the blood serum at the time of the test. It has, however, been found necessary to exclude serum lipase results obtained from lysed sera, which gave abnormally low readings.

We have, as far as possible, carried out an oral glucose tolerance test in the patients suffering from pancreatic disease, following the observation that in cancer of the pancreas progressive deterioration of endocrine function was not infrequent. It soon became apparent that the evocative test was less likely to be positive when glucose tolerance was impaired than when glucose tolerance was normal. It appears, therefore, that when glucose tolerance is impaired to a considerable extent due to pancreatic disease appreciable destruction of acinar function has also taken place. The fasting serum enzyme also is less likely to be elevated when glucose tolerance is impaired. Lopusniak and Bockus (1950), using secretin alone, have already noted the converse of this statement, that a greater elevation of serum amylase and lipase was evoked in those patients with pancreatic disease in whom the resting serum enzymes were raised. A comparison has been made between the significance of the mean control and mean maximal post-stimulation values. It is important to note that value of "t" is always very much greater for the peak mean than the control mean in those groups where this value is significant. This underlines the value of stimulation as practised in this simple evocative test. In many cases duodenal intubation has been performed, and a correlation of the evocative test and duodenal volume in chronic pancreatitis and cancer of the pancreas indicates that a positive evocative test is seen more frequently when the duodenal output is adequate than when it is diminished. There is a striking difference between the mean results of the inflammatory and the malignant cases with low duodenal volume, the enzyme levels being much higher in the malignant cases (Figs. 3 and 4). This suggests that in carcinoma of the pancreas a low duodenal volume is less clearly indicative of extensive acinar damage, which presumably develops relatively slowly after early obstruction of the duct in these cases. A positive correlation in chronic pancreatic disease, both cancer and pancreatitis, also exists between the diabetic state and a low volume of duodenal contents in response to stimulation of the pancreas.

Patients who have had acute pancreatitis and recovered may show no functional derangement of the gland. It seems worthy of note, however, that those patients stimulated within 10 days of an acute attack of mild or moderate severity and still showing an elevated fasting amylase or lipase in serum have responded in a characteristic manner, the level continuing at about control level throughout the test, and remaining at this raised level at 24 hours. This pattern of response may be related to the increased acinar-capillary permeability shortly after an acute attack of pancreatitis (Sun and Shay, 1957). Apart from those cases only a few tests in this group have been positive. Of these permanent damage may have been present in the pancreas in one or two which more correctly might find a place in the chronic pancreatitis group. In some others coexisting disease of the biliary tract may have been a factor in producing the positive evocative test.

The group with biliary tract disease includes a considerable number of diabetic patients, but in this instance there was no reason to attribute the impaired glucose tolerance to pancreatic disease. In contrast to the findings in chronic pancreatic disease, in biliary and liver disease the proportion of positive evocative tests in non-diabetic patients is the same as the proportion in diabetic patients.

The evocative tests are more frequently positive in association with stone and stricture of the bile ducts when the gall bladder is present than when it has been removed, an indication that in addition to the mechanical factors of stone or stricture of the bile ducts impeding pancreatic flow, contraction of the sphincter may play a part, since the sphincteric mechanism is destroyed by cholecystectomy. Positive evocative tests have been obtained even with no evidence of stone in the common bile duct. A few of these may be instances of mild pancreatitis, but stones in the neck of the gall bladder or impacted in the cystic duct were thought to be particularly liable to cause a rise in serum enzymes. The close association of gall bladder and pancreatic disease is again emphasized by these results.

A surprising feature has been the number of positive evocative tests obtained in cancer sited primarily in the bile ducts. That early ampullary cancer should give a marked response is not unexpected. In a few instances the primary site may have been thought to be in the lower common duct whereas in fact the tumour was pancreatic or the pancreatic duct may have been involved in the tumour at an early stage; in three patients with positive tests gall stones were present in addition to cancer. The positive tests were not associated with secondary deposits in the liver visible to the naked eye, nor was the amount of bile in the serum thought to be a factor in determining the higher number of positive lipase tests compared with amylase tests (a ratio of 6 to 1) for reasons already stated. Duodenal intubation was done on three patients with biliary cancer, none of whom gave a positive evocative test, and an adequate volume was obtained from all three. The fact remains that the evocative test alone cannot be used to distinguish bile duct cancer from primary cancer of the pancreas.

In the two instances when the pancreas was involved secondarily by cancer of the stomach positive tests were obtained. Positive evocative tests were also encountered in a patient with cancer of the bronchus and another patient with cancer of the rectum. These results were accounted for by growth involving the para-aortic glands in close relation to the pancreas. Raised serum lipase values have been reported in advanced metastatic cancer of the liver, when the primary tumour was in the bronchus (Edmondson, Berne, Homann, and Wertman, 1952) and in the colon (Johnson and Bockus, 1940). Neither of our patients had detectable secondary deposits in the liver at the time of the test.

Johnson and Bockus (1940) and Cummins and Bockus (1951) report raised serum lipase values in liver damage even when there is no pancreatitis. We have found positive evocative tests in three of 11 patients with cirrhosis of the liver, in two of whom both amylase and lipase were abnormal, in the third lipase only. Cummins and Bockus have suggested three possible mechanisms to account for the elevation of these enzymes in the serum of cirrhotics: that the enzymes are released from damaged hepatic cells, that an enzyme destroying mechanism present in normal liver fails, and that mild pancreatitis coexists. High enzymes in serum may also be additional evidence of the development of anastomoses between the portal and systemic circulations.

We have encountered raised amylase and lipase values after stimulation in a patient with ileal ulceration, steatorrhoea, and advanced renal failure due to chronic pyelonephritis. Dankner and Heifetz (1951) report increased serum enzymes in renal failure with nitrogen retention, though Gross and Comfort (1956) have found normal values in this condition. In a study of 50 patients with uraemia we have encountered raised values for serum amylase and lipase in nine of the 14 patients in whom the blood urea exceeded 375 mg. per 100 ml. (Burton, Eddleston, Howat, and Wilson, 1959). This, essentially a terminal event, was not a factor responsible for the raised enzymes in any other patient in this series.

Knight *et al.* (1949), who did serial estimations of serum amylase at 30-minute intervals over two

hours following the injection of 1 mg. of prostigmin methyl sulphate intramuscularly, have analysed the curve of response in an attempt to draw conclusions about the degree of obstruction and pancreatic secretory capacity. This does not always seem possible from information gleaned solely from the evocative test, although early obstructive pancreatic lesions such as ampullary cancer may give normal resting values and a considerable rise following stimulation. Should no rise occur or even a fall result, the interpretation of an essentially functional test in anatomical terms becomes more speculative. It seems more rewarding to obtain evidence of diminished pancreatic function from a collection of duodenal contents as proposed by Sun and Shay (1957). Our results suggest that evocative tests provide earlier information of pancreatic derangement than does examination of the duodenal contents which are progressively diminished in enzyme output, bicarbonate, and finally volume as pancreatic disease progresses. From the data of this study it has been possible, by using a simple oral glucose tolerance test, to establish a direct relationship between impaired glucose tolerance and diminished volume of pancreatic secretion and an inverse relationship with positive evocative function tests. Estimation of glucose tolerance and evocative tests in which secretin and pancreozymin are used as pancreatic stimulants show some overlap (Burton, Hammond, Harper, Howat, Oleesky, and Varley, 1956), and together indicate chronic pancreatic disease in a considerable proportion of patients. In the combined groups of cancer of the pancreas and chronic pancreatitis of this present series, an indication of the presence of pancreatic disease has been obtained in all but four of 57 patients, using the evocative test in conjunction with the oral glucose tolerance test.

False positive evocative tests do occur in relation to biliary tract disease, occasionally in cancer not involving the pancreas, in cirrhosis of the liver, and in the terminal stages of uraemia. Such exceptions serve as a reminder that function tests should be interpreted only in terms of function and that before anatomical or pathological interpretations are made, a careful correlation with other clinical and biochemical data is necessary. The association of positive evocative tests with biliary disease, and especially with lesions of the common bile duct, re-emphasizes the close functional, developmental, and anatomical relationship between the bile ducts and pancreatic ducts, and the frequent association of biliary and pancreatic disease.

We are grateful to Miss Josephine Smith who undertook some of the chemical determinations for this study.

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# LEUCINE AMINOPEPTIDASE WITH SPECIAL REFERENCE TO ULCERATIVE COLITIS

BY

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It has been suggested that ulcerative colitis might be associated with excessive production of histamine released locally from mast cells. These cells also contain a proteolytic enzyme, leucine aminopeptidase, which might also be released at the same time if this hypothesis were correct. The studies reported do not invalidate this concept of aetiology in ulcerative colitis but provide no positive evidence in support of it.

Leucine aminopeptidase is a proteolytic enzyme which is capable of hydrolysing L-leucyl peptides and is widely distributed throughout the body. The level of this enzyme in the serum is usually much raised in obstructive jaundice from cancer of the pancreas but this reaction is not constant and aminopeptidase is elevated to a lesser extent in other forms of jaundice. Moreover, very high values are normally found in the third trimester of pregnancy (Rutenburg, Goldbarg, and Pineda, 1958; Arst, Manning, and Delp, 1959; Bressler and Forsyth, 1959).

The tissue mast cells give a histochemical reaction for leucine aminopeptidase. When tissues containing many mast cells are exposed to hypotonic solutions *in vitro*, the mast cells rupture and there is an increase of aminopeptidase in the surrounding fluid. The human skin in urticaria pigmentosa is infiltrated with mast cells and friction of the affected areas may produce an increase of leucine aminopeptidase in the serum (Braun-Falco and Salfeld, 1959).

The mast cells contain other important constituents besides aminopeptidase, in particular heparin, histamine, and 5-hydroxytryptamine. A number of pharmacological agents are known which cause histamine to be released within the organism and all of these cause swelling, degranulation, and even disruption of the mast cells (Riley, 1959). Mast cells are increased in the tissues in chronic inflammation, and McGovern (1956) suggested that the permeability of serous membranes might be related to their activity. Subsequently, McGovern and Archer (1957) discussed the pathogenesis of ulcerative colitis in terms of histamine-release phenomena. They suggested that augmented barrages of nervous impulses during stress might give rise to excessive production of acetylcholine in the colon, which would then react with the tissue mast cells causing release of histamine. We felt that if this hypothesis were correct, aminopeptidase should also be released and might be detected in the blood stream. With this objective in view we have estimated leucine aminopeptidase in the serum in ulcerative colitis and other conditions.

## Methods

The method of Goldbarg and Rutenburg (1958) was used. This depends on the enzymatic hydrolysis of L-leucyl-$\beta$-naphthylamide hydrochloride and the estimation of the $\beta$-naphthylamine released by a modification of the Bratton-Marshall reaction. It was found that the final colour reaction was photosensitive and estimations were therefore carried out in a darkened laboratory. The results were expressed in units, each unit being equivalent to 1 $\mu$g. of $\beta$-naphthylamine liberated from 200 $\mu$g. of L-leucyl-$\beta$-naphthylamide after incubation with 1 ml. of 2% serum for two hours at 37°C. These units should be multiplied by 12 if it is desired to convert them to the arbitrary units used by Goldbarg and Rutenburg (1958). Our unit is also different from that used by Arst *et al.* (1959), whose mean normal value for serum was 100 units.

## Results

Leucine aminopeptidase was estimated in the serum of normal persons and patients with ulcerative colitis, jaundice, and other diseases. Normal levels averaged 16 units, with a range of 10 to 31 units. Levels in 31 patients with ulcerative colitis were normal, the mean being 19 and the range 11 to 34 units. High levels were found only in patients with jaundice. The highest levels were in jaundice

TABLE

SERUM LEUCINE AMINOPEPTIDASE ACTIVITY IN VARIOUS CONDITIONS

| | No. | Range | Mean | S.D. |
|---|---|---|---|---|
| Normals | 19 | 10–31 | 16 | 5 |
| Ulcerative colitis | 31 | 11–34 | 19 | 9 |
| Various diseases including leukaemia | 25 | 9–37 | 22 | 7 |
| *Jaundice* | | | | |
| Infective hepatitis | 2 | 20–32 | 26 | — |
| Weil's disease | 1 | — | 38 | — |
| Non-malignant obstructive jaundice | 9 | 21–60 | 36 | — |
| Carcinoma of pancreas | 7 | 32–78 | 51 | — |
| Carcinoma of gall-bladder | 1 | — | 77 | — |

due to malignant disease but a high value of 60 units was noted in a patient with non-malignant obstructive jaundice. This was a post-operative estimation and Goldbarg and Rutenburg (1958) have observed a post-operative rise in serum leucine aminopeptidase.

In view of the normal findings in ulcerative colitis, it was decided to see if the serum aminopeptidase was, in fact, increased in experimental animals after the phenomenon of histamine release. The mean level in 30 normal rats was 14, with a range of 11 to 18 units. Eight rats were given an intraperitoneal injection of 100 $\mu$g. of the histamine liberator, compound 48/80, and the serum aminopeptidase was estimated at intervals during the subsequent two-and-a-quarter hours. A few minutes after the injection the animals showed signs of shock with cyanosis of the ears. There was no change in serum aminopeptidase activity.

| Time (min.) | No. of Estimations | Mean Value |
|---|---|---|
| 0 | 4 | 14 |
| 5 | 2 | 14 |
| 15 | 2 | 12 |
| 45 | 2 | 11 |
| 135 | 2 | 10 |

In a subsequent experiment 300 $\mu$g. compound 48/80 was injected intraperitoneally in rats and estimations were carried out at intervals during the subsequent 24 hours. Again there was no change in the serum aminopeptidase.

| Time (hr.) | No. of Estimations | Result |
|---|---|---|
| 0 | 1 | 14 |
| 1 | 1 | 15 |
| 2 | 1 | 12 |
| 4 | 1 | 11 |
| 8 | 1 | 12 |
| 24 | 1 | 16 |

## DISCUSSION

Our experiments have confirmed the reports of other workers that leucine aminopeptidase is increased in the serum of patients with obstructive jaundice, particularly when this is due to carcinoma. We have found no increase in chronic ulcerative colitis. This result does not necessarily invalidate the hypothesis of McGovern and Archer (1957) that ulcerative colitis may be a histamine-release phenomenon, associated with discharge of the contents of the mast cells in the colon, for, although heparin and leucine aminopeptidase should be simultaneously released, it does not follow that they will pass into the blood stream. Previous workers have shown that there is no rise of heparin in the blood of the rat after the injection of histamine liberators and we have shown that there is likewise no increase in leucine aminopeptidase. It therefore seems probable that further testing in man of McGovern and Archer's hypothesis will have to be made on specimens from the affected colon itself.

We are indebted to Dr. A. C. White of the Wellcome Research Laboratories for a supply of 48/80 histamine liberator.

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# EFFECT OF GLUCAGON ON GASTRIC SECRETION IN MAN

BY

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Glucagon suppresses gastric acid secretion in normal subjects and in ulcer patients. It has no inhibitory effect while the stomach is under maximal histamine stimulation. The mechanism of action is discussed, and experiments are described which indicate that glucagon is unlikely to be of value in the treatment of peptic ulcer.

Glucagon, the hyperglycaemic-glycogenolytic factor of the pancreas, was discovered and named in 1923, but only recently, following its preparation in pure crystalline form (Staub, Sinn, and Béhrens, 1953), has it been possible to accord to glucagon the status of a true hormone. A complete structure analysis of the glucagon molecule has been achieved (Bromer, Sinn, Staub, and Béhrens, 1956), and is quite different from that of insulin. With the alpha cells of the islets of Langerhans as its source (Korp and Lecompte, 1955; Bencosme and Frei, 1956), glucagon raises the blood sugar by promoting glycogenolysis in the liver, and this in turn is due to activation of liver phosphorylase: there is no effect on muscle glycogen (Sutherland and Cori, 1948). The physiological role of glucagon, and recent developments in glucagon research, have been reviewed by Elrick, Staub, and Maske (1957), by Béhrens and Bromer (1958), and by Lukens (1959). When pure glucagon became available in small quantities for experimental purposes it was observed that the hormone produced metabolic and clinical effects unrelated to the action on hepatic glycogen. The renal excretion of electrolytes is enhanced (Staub, Springs, Stoll, and Elrick, 1957) and large doses have a protein catabolic effect (Ezrin, Salter, Ogryzlo, and Best, 1957). A suggestion (Summerskill, 1959) that glucagon might be the ulcerogenic factor in the syndrome described by Zollinger and Ellison (1955) has not been confirmed. In this syndrome, which is characterized by recurrent intractable multiple peptic ulceration, marked gastric hypersecretion, and the presence in most cases of alpha cell pancreatic tumours, the aetiology is still unknown: the observation by Fisher and Flandreau (1957) that, in a patient dying of this syndrome, a hyperglycaemic substance with some similarity to glucagon could be isolated from one of the alpha cell tumours had also stimulated interest in the possible effect of glucagon on the stomach. It has been reported (*e.g.*, Elrick *et al.*, 1957) that glucagon has an inhibitory effect on gastric secretion; in this communication experiments are described which confirm these reports and were undertaken to aid in the elucidation of the mode of action of the hormone on the stomach. The striking and consistent inhibitory effect of glucagon on spontaneous gastric secretion has suggested the possibility that it will prove useful in the treatment of peptic ulcer, and the potential value of the hormone in the management of this disease has also been investigated.

## Methods

In seven fasting patients, who had no alimentary symptoms and were free from any disease known to affect gastric secretion, a small-bore stomach tube was passed and the resting juice removed. With continuous gastric suction and the patient positioned on the left side gastric juice was collected for one hour. Glucagon, 0·01 mg. per kg., was injected intravenously and the collection proceeded for a second one-hour period. The samples were measured and titrated for free acidity. In all the following investigations patients with radiologically proven chronic duodenal ulcer were used. The investigations described above were repeated in five ulcer subjects. The augmented histamine test meal (Kay, 1953) was carried out in seven patients, and the maximum histamine response (M.H.R.) determined. Several days later the test was repeated, injecting glucagon, 0·02 mg. per kg. intravenously, at the beginning of the half-hour collection period. This investigation was repeated using another group of ulcer patients and doses of glucagon four times as great, *i.e.*, 0·08 mg. per kg. intravenously. Using doses of 0·01-0·02 mg. per kg., moderate hyperglycaemic responses of about 30 mg.% of glucose were

obtained, indicating a definite response to the hormone. There were no side-effects and glycosuria was not observed in any test.

In 10 ulcer patients a Ryle's tube was passed nasally into the stomach and retained in position for 24 hours. Ordinary ward diet was allowed, the patients were permitted to move about the ward at will, and no drug treatment was given. Specimens of gastric juice were aspirated hourly for testing *p*H, positioning the patient as required to facilitate removal. During the 24-hour period glucagon, 1 mg. intramuscularly, was given at intervals of eight hours.

## Results

Glucagon had an inhibitory effect on the spontaneous gastric secretion of hydrochloric acid both in non-ulcer and in ulcer patients (Figs. 1 and 2). In Figs. 3 and 4 it is seen that the maximum histamine response of acid output is unaltered by glucagon in dosage of either 0·02 or 0·08 mg. per kg. ($t<1$ in each case). Of the 24-hour test meal specimens, those collected immediately before and one hour after glucagon injection may have been expected to reveal any changes in *p*H attributable to the hormone, and 27 paired results were available for statistical analysis (Table I), which fails to reveal any significant difference ($t<1$). In eight tests there was no change in *p*H, in 12 a fall occurred, and in only seven did the *p*H rise. The results in a typical case are shown in Fig. 5.

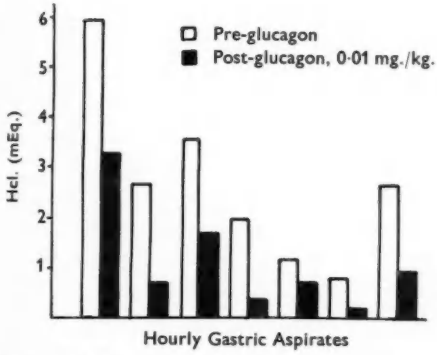


FIG. 1.—*Inhibitory effect of glucagon on spontaneous gastric acid secretion in seven normal subjects.*

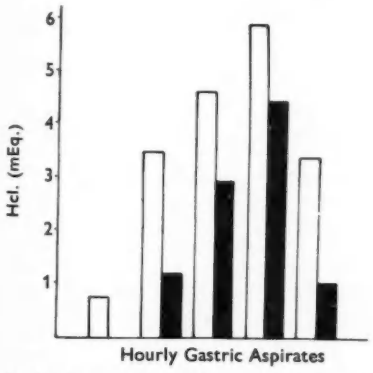


FIG. 2.—*Inhibitory effect of glucagon on spontaneous acid secretion in five duodenal ulcer patients (dosage as in Fig. 1).*

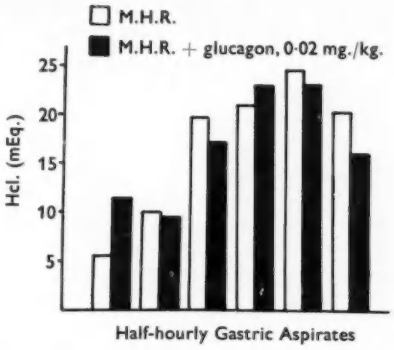


FIG. 3.—*Failure of inhibitory effect of glucagon on maximum histamine response (M.H.R.) of acid output during augmented histamine test meal (glucagon 0·02 mg./kg.) in six male duodenal ulcer patients.*

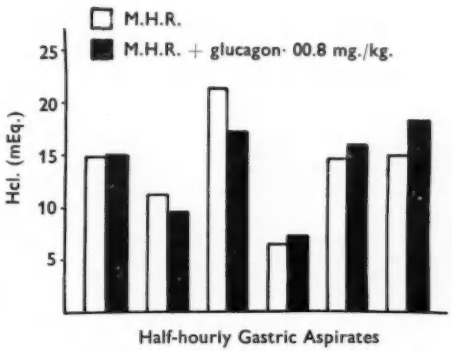


FIG. 4.—*Failure of inhibitory effect of glucagon on maximum histamine response (M.H.R.) of acid output during augmented histamine test meal (glucagon 0·08 mg./kg.) in six male duodenal ulcer patients.*

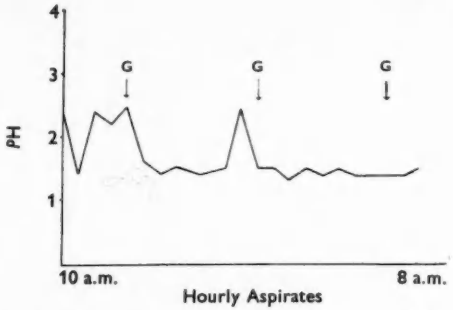


FIG. 5.—*Gastric juice pH recordings over a 23-hour period. Effect of glucagon, 1 mg. intramuscularly at eight-hour intervals, in a case of duodenal ulcer.*

TABLE I

EFFECT OF GLUCAGON ON *p*H OF GASTRIC JUICE

| No. of Test | Before Glucagon | After Glucagon | *p*H Change |
|---|---|---|---|
| 1 | 3 | 2·1 | −0·9 |
| 2 | 1·1 | 1·1 | 0 |
| 3 | 1·6 | 1·6 | 0 |
| 4 | 1·4 | 1·9 | +0·5 |
| 5 | 1·5 | 1·4 | −0·1 |
| 6 | 1·7 | 1·7 | 0 |
| 7 | 1·6 | 5·0 | +3·4 |
| 8 | 1·6 | 1·3 | −0·3 |
| 9 | 4·4 | 4·1 | −0·3 |
| 10 | 1·8 | 1·8 | 0 |
| 11 | 2·6 | 2·2 | −0·4 |
| 12 | 5·7 | 5·2 | −0·5 |
| 13 | 3·3 | 3·1 | −0·2 |
| 14 | 3·6 | 3·5 | −0·1 |
| 15 | 1·5 | 1·5 | 0 |
| 16 | 1·3 | 1·5 | +0·2 |
| 17 | 6·8 | 1·8 | +5·0 |
| 18 | 1·9 | 1·7 | −0·2 |
| 19 | 1·6 | 1·6 | 0 |
| 20 | 6·1 | 3·3 | −2·8 |
| 21 | 5·1 | 6·4 | +0·7 |
| 22 | 1·9 | 1·8 | −0·1 |
| 23 | 1·8 | 2·1 | +0·3 |
| 24 | 3·4 | 4·0 | +0·6 |
| 25 | 2·5 | 1·6 | −0·9 |
| 26 | 1·5 | 1·5 | 0 |
| 27 | 1·4 | 1·4 | 0 |

## DISCUSSION

Inhibition of gastric motility in man by glucagon has been reported by Stunkard, Van Itallie, and Reis (1955), and in the experimental animal by Mayer and Sudsaneh (1959). The latter authors consider that the hyperglycaemia, acting on a glucoreceptor area in the ventromedial hypothalamus, results in vagal inhibition. A fall in blood pepsinogen levels in the dog and in man was recorded by Earle, Cahill, and Hoar (1957). The effect of glucagon on acid gastric secretion was studied by Robinson, Harris, Hlad, and Eiseman (1957) in seven subjects, four of whom had peptic ulcer, and a fall in acid output was noted in each case. Elrick *et al.* (1957) also state that the hormone has a marked inhibitory effect on resting gastric secretion, and preliminary but confirmatory investigations were reported by Dall and Melrose (1959). Twenty-four patients were studied by Dreiling and Janowitz (1959), who noted that glucagon caused depression of the rate of volume flow, acid formation, and pepsin secretion in gastric juice. Free acid secretion was completely inhibited in non-ulcer patients, but acid was not completely suppressed in ulcer subjects. The inhibitory effect was observed to last for up to five hours, and its existence in relation to spontaneous gastric secretion is now well established.

It is unlikely that the hyperglycaemia induced by glucagon takes part in the mechanism by which acid gastric secretion is inhibited. The hyperglycaemic period is brief, lasting 60 to 75 minutes, in contrast to the prolonged duration of acid suppression. Solomon and Spiro (1960) compared the acid inhibitory effects of intravenous infusions of glucose and of glucagon, and noted that glucose-induced acid suppression was very slight in degree while that of glucagon was marked. It has not been possible to demonstrate a local inhibitory effect of glucagon within the gastric mucosa. Irrigation of the stomach with glucagon solutions has no effect on gastric secretion, nor would any be expected, since glucagon is destroyed by the peptic activity of gastric juice. A local suppressive action of glucagon on the parietal cell population may be assumed if the hormone can be shown to inhibit the acid response to histamine, and the investigations of Cohen, Mazure, Dreiling, and Janowitz (1959) are of interest. Using varying doses of glucagon and histamine given together, they reported that some inhibition of acid output could be achieved when the dose of histamine was small: larger doses of histamine were associated with smaller degrees of inhibition, which was markedly less in the second 20 minutes than in the first 20 minutes after injection of glucagon with prior histamine stimulation. Scrutiny of their data suggests that glucagon can produce a degree of inhibition during submaximal histamine stimulation; during the period of maximal histamine response, as defined by Kay (1953), and as studied in the present communication, glucagon fails to suppress acid gastric secretion. It is concluded that glucagon does not have a direct action on gastric mucosa, and the hormone may interfere with the regulatory mechanism for gastric secretion.

The suppressive effect of glucagon on gastric secretion has led Solomon and Spiro (1960) to speculate on its potential application in the treatment of peptic ulcer. Long-term administration would be required, and the possibility that chronic glucagon administration could induce a permanent diabetic state in man has not yet been completely excluded.

Large doses of glucagon have a catabolic effect, and the need for frequent injections would be a disadvantage. Eight-hourly injections of glucagon given while simulating normal activities and normal diet in 10 patients (subject to experimental conditions) have failed to produce significant elevation of the *p*H of gastric juice, and the results compare unfavourably with conventional methods of treatment. The provisional findings are not encouraging and it seems unlikely that glucagon will be found of value in the management of peptic ulcer.

I wish to thank Dr. L. D. W. Scott and Professor C. F. W. Illingworth for advice, and Dr. R. A. Robb for the statistical analyses. Glucagon was supplied by Messrs. Eli Lilly and Co. Ltd.

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*Gut*, 1960, **1**, 146.

# EFFECT OF GLUCAGON ON GASTRIC SECRETION IN THE DOG*

BY

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The effects of glucagon on gastric secretion in the dog have been studied. Gastric juice was collected both from denervated and innervated pouches under basal conditions and when the animals were stimulated by meat extract and by histamine. In the dogs with innervated pouches psychic stimulation and the stimulatory action of insulin-induced hypoglycaemia were also used.

Glucagon reduced the volume but not the acidity of gastric juice collected under all conditions. This effect was independent of its hyperglycaemic action and occurred when physiological doses were administered.

Soon after the discovery of insulin it was noted that certain extracts of the pancreas induced a rise, instead of the usual fall, in the blood sugar level. This activity was attributed to a hypothetical hyperglycaemic factor, to which the name "glucagon" was given (Murlin, Clough, Gibbs, and Stokes, 1923). Glucagon has now been isolated and analysed and it is probable, though not certain, that it is formed in the alpha cells of the Islets of Langerhans.

In the Zollinger-Ellison syndrome a tumour of the islet cells is associated with gross gastric hypersecretion and with fulminating peptic ulceration. While most of these tumours do not secrete insulin, it is possible that they secrete a humoral agent which stimulates the production of acid and thus causes the ulcers. The tumours are usually composed of alpha cells (Gibson and Welbourn, 1960), and it has been suggested that they secrete glucagon and that this is the cause of the hyperacidity (Zollinger and Ellison, 1955; *Lancet*, 1959). This suggestion led several workers to investigate the effects of glucagon on gastric function.

It had been noted already that the intravenous administration of insulin caused a decrease in gastric secretion before the usual hypersecretory response (Olson and Necheles, 1953). It seems possible, in the light of later work, that this was the result of contamination of the insulin by glucagon. Glucagon reduces the volume and the acidity of the basal secretion in man (Robinson, Harris, Hlad, and Eiseman, 1957; Dall and Melrose, 1959; Dreiling and Janowitz, 1959) and it abolishes the acid secretory response to a meal and to insulin in the dog (Lin and Alphin, 1958). The response to histamine is reduced by glucagon in man (Cohen, Mazure, Dreiling, and Janowitz, 1959) but not in the dog (Lin and Alphin, 1958). Glucagon reduces the secretion of pepsin in the gastric juice in man (Cohen *et al.*, 1959; Dreiling and Janowitz, 1959) and lowers the concentration of pepsinogen in the blood in man and in the dog (Earle, Cahill, and Hoar, 1957). It also reduces gastric motility (Stunkard, Van Itallie, and Reis, 1955; Robinson *et al.*, 1957).

It has been suggested that the inhibitory effect is secondary to the concomitant hyperglycaemia. Some (Earle *et al.*, 1957) observed a similar depression of gastric secretion when they injected glucose intravenously, but others (Stunkard *et al.*, 1955; Robinson *et al.*, 1957) found that the period of inhibition corresponded to that when the difference between the concentration of glucose in the arterial or capillary blood and that in the venous blood was greatest. Others (Cohen *et al.*, 1959) failed to correlate the inhibition with the blood glucose level.

This investigation was undertaken to determine: (1) The effects of glucagon on the volume and acidity of gastric juice in the dog under different conditions; (2) the relation of gastric secretion to the blood glucose level; (3) the doses of glucagon which would influence the stomach and the blood glucose level respectively.

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## MATERIALS AND METHODS

Six smooth-haired mongrel bitches, weighing 7·8 to 11·9 kg., were used. Denervated (Heidenhain) pouches were prepared in four and innervated (Pavlov) pouches (Gregory, Hallenbeck, and Code, 1942) in two. They were fitted with "duralumin" cannulae. The animals were not tested for at least five weeks after operation. They were fed on a standard diet of meat offal and pig starter meal in equal parts. Each dog was fed once daily with a measured quantity sufficient to provide approximately 70 calories per kg. per day. They were fasted for 18 hours before each test.

Gastric juice was collected in graduated tubes. The volume was read off directly and the *p*H was measured on a direct-reading *p*H meter. Except when stated otherwise, the juice was collected for half an hour. Collections were made under the following conditions.

### Both Types of Pouch

(1) Basal Secretion.—In these tests the gastric juice was collected for four hours from the unstimulated pouch.

(2) Antral Stimulation.—The gastric antrum was stimulated by the injection of meat extract (35 ml. of a 20% solution of "bovril" at *p*H 5·4) into the stomach through a polythene tube.

### Denervated Pouches Only

(3) Histamine Stimulation.—Histamine acid phosphate (B.P.) was injected subcutaneously in a dose of 1 mg. histamine base per 10 kg. body weight. Half an hour before the administration of histamine 5 mg. of chlorpheniramine maleate (an antihistaminic drug) was given subcutaneously. Collections were started after the injection of histamine.

### Innervated Pouches

(4) Psychic Stimulation.—Three types of stimuli were combined.

*Sight.*—The meal was placed within sight, but out of reach, of the dog.

*Smell.*—A solution of meat extract was boiled in the room.

*Taste.*—One lick of a spoon lightly smeared with meat extract.

The technician who usually fed the dogs was present in the room during the tests.

(5) Hypoglycaemic Stimulation.—Soluble insulin was given intravenously in doses of 20 or 40 units. Glucose (40 ml. of 50% solution) was given orally after the tests to prevent severe hypoglycaemic reactions.

### Dosage of Glucagon

Crystalline glucagon in an aqueous solution was injected intravenously. The dose was 1·0 mg. except where stated otherwise. Its injection did not cause any rise in the rectal temperature. Varying doses of glucose, in a 50% aqueous solution, were injected intravenously.

Blood glucose estimations were made by a micro-modification of the method of Folin and Wu (1920), suitably altered to yield "true glucose" values.

## RESULTS

### Effect of Glucagon on Secretion from Denervated Pouches

Glucagon reduced the volume of the secretion under basal conditions and when stimulated by meat extract. It did not influence the histamine-stimulated secretion significantly (Table I). There was no consistent effect on the acidity.

Table I

EFFECT OF GLUCAGON ON GASTRIC SECRETION FROM DENERVATED POUCHES*

| | Control | Glucagon | Mean % Difference† |
|---|---|---|---|
| Volume (ml./½ hour) | | | |
| Unstimulated | 0·63‡ (27) | 0·32 (8) | − 52·5 |
| Increase with:* | | | |
| Meat extract | 3·61 (22) | 0·42 (7) | − 78·8 |
| Histamine | 10·24 (22) | 8·94 (8) | − 12·0 |
| *p*H | | | |
| Unstimulated | 5·5 (27) | 4·8 (8) | − 13 |
| Meat extract | 1·7 (22) | 2·5 (7) | + 38 |
| Histamine | 1·3 (22) | 1·4 (8) | + 4 |

*Stimulated minus unstimulated volume.
†Glucagon minus control values.
‡All figures are the averages of the means for the 4 dogs.
Number of tests shown in brackets.

### Effect of Glucagon on Secretion from Innervated Pouches

Glucagon did not affect the volume of the basal secretion (which was very low). It abolished the secretory response to psychic stimuli and reduced appreciably the responses to hypoglycaemia and to meat extract. Insulin (20 units) overcame the hyperglycaemic effect of the glucagon and produced blood sugar levels of 26 to 31 mg. per 100 ml. There was no consistent effect on the acidity.

Table II

EFFECT OF GLUCAGON ON GASTRIC SECRETION FROM INNERVATED POUCHES

| | Control | Glucagon | Mean % Difference† |
|---|---|---|---|
| Volume (ml./½ hour) | | | |
| Unstimulated | 0·5‡ (11) | 0·5 (5) | 0 |
| Increase with:* | | | |
| Psychic stimulation | 2·25 (11) | 0·0 (6) | − 100 |
| Insulin | 3·9 (8) | 1·4 (6) | − 65 |
| Meat extract | 6·7 (7) | 1·8 (6) | − 69 |
| *p*H | | | |
| Unstimulated | 5·9 (11) | 6·0 (5) | + 3 |
| Psychic stimulation | — | — | — |
| Insulin | 2·0 (8) | 2·0 (6) | 0 |
| Meat extract | 2·9 (7) | 3·1 (6) | + 15 |

*Stimulated minus unstimulated volume.
†Glucagon minus control values.
‡All figures are the averages of the means for the 2 dogs.
Number of tests shown in brackets.

### Effects of Glucose and Glucagon Plus Insulin on Secretion from Denervated Pouches

Glucose, given intravenously in doses between 2·7 and 15·0 g., produced blood sugar curves similar

to those which followed glucagon (1·0 mg.) (Table III). It did not, however, reduce the volume or the acidity of the unstimulated secretion or that

TABLE III

EFFECT OF GLUCAGON (1·0 mg.) AND OF GLUCOSE (10 g.) ON BLOOD SUGAR IN A TYPICAL EXPERIMENT

| Time (min.) | 0 | 15 | 30 | 45 | 60 |
|---|---|---|---|---|---|
| Blood glucose (mg./100 ml.) | | | | | |
| Glucagon | 68 | 125 | 104 | 89 | 64 |
| Glucose | 71 | 134 | 115 | 94 | 78 |

This effect of glucagon on the stomach is probably a direct one and not a result of hyperglycaemia. Glucose, which raised the blood sugar level to the same extent as glucagon, did not influence the secretion, and glucagon still greatly reduced the response to meat extract when hyperglycaemia was prevented by insulin.

The fact that glucagon affects the stomach in doses similar to those which raise the blood sugar suggests that it may play a part in the physiological

TABLE IV

EFFECT OF GLUCOSE ON GASTRIC SECRETION FROM DENERVATED POUCHES

| | Control | | | Glucose | | |
|---|---|---|---|---|---|---|
| | No. of Tests | Volume (ml./½hr.) | *p*H | No. of Tests | Volume (ml./½hr.) | *p*H |
| Unstimulated | 5 | 0·6* | 5·8 | 2 | 0·5 | 3·2 |
| Stimulated with: | | | | | | |
| Meat extract | 5 | 3·3 | 1·7 | 4 | 5·4 | 1·2 |
| Histamine | 5 | 7·9 | 1·2 | 1 | 9·0 | 1·2 |

*All figures are mean values. The small differences are not statistically significant.

TABLE V

EFFECT OF GLUCAGON AND INSULIN TOGETHER ON MEAT-EXTRACT-STIMULATED SECRETION FROM DENERVATED POUCHES

| | Dog 201 | | | Dog 202 | | |
|---|---|---|---|---|---|---|
| | No. of Tests | Volume (ml./½hr.) | *p*H | No. of Tests | Volume (ml./½hr.) | *p*H |
| Control | 5 | 3·0* | 1·7 | 5 | 1·3 | 2·0 |
| Glucagon and insulin | 4 | 1·2 | 2·2 | 1 | 0·6 | 3·3 |

*All figures are mean values.

induced by meat extract or histamine (Table IV). In a further experiment, in which meat extract was used as the gastric stimulant, insulin (40 units) was given 15 minutes before the glucagon to prevent a rise in the blood sugar. Secretion was still inhibited (Table V).

### EFFECTS OF VARYING DOSES OF GLUCAGON ON BLOOD SUGAR AND ON GASTRIC SECRETION

Secretion in response to meat extract was greatly reduced by glucagon in a dose of 0·1 mg. (one tenth of that used in 1-3 above), but was not affected when the dose was reduced to 0·05 mg. or 0·01 mg. A significant rise in the blood sugar (8 mg. per 100 ml.) was produced by doses of 0·05 mg. and more, but not by 0·01 mg.

## DISCUSSION

Glucagon reduces the volume of gastric secretion under basal conditions and after all the forms of stimulation which were used. (The volume of the unstimulated juice from the innervated pouches was too low for any differences to be detected.) It does not, apparently, affect the acidity, indicating that the composition of the juice (in this respect) is unchanged. It is, therefore, very unlikely that glucagon is the cause of gastric hypersecretion in the Zollinger-Ellison syndrome.

regulation of gastric secretion. Glucagon is probably secreted maximally during the fasting state to prevent hypoglycaemia. It would certainly perform a useful function if, at the same time, it tended to prevent the secretion of gastric juice by the empty stomach.

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*Gut*, 1960, **1**, 149.

# PARTIAL GASTRECTOMY FOR PEPTIC ULCER

BY

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This paper reports a study of 955 patients in whom partial gastrectomy was performed for peptic ulcer. An analysis is presented of the clinical and operative factors which may influence the success of the operation.

In a recent investigation undertaken by us to determine the incidence of pulmonary tuberculosis in patients who had undergone partial gastrectomy for ulcer (Thorn, Brookes, and Waterhouse, 1956), the opportunity was taken to collect as much information as possible regarding the results of gastrectomy for ulcer. An attempt is made in this paper to assess these results, and to analyse the factors influencing them.

## MATERIAL

The information collected concerned all patients in whom a gastrectomy for peptic ulcer was carried out by the surgeons attached to the Surgical Professorial Unit of Birmingham University (at the Queen Elizabeth Hospital) between the beginning of 1948 and the middle of 1953. In addition to the information available from previous interviews at a routine gastrectomy follow-up clinic, two of us (B and T) further interviewed and examined as many of these patients as could be traced. In a small number, where personal interview was not possible, information was collected by questionnaire.

The figures obtained were analysed with the aid of a punch card system under the supervision of the Medical Statistics Department of Birmingham University (W).

Cases were not selected for the investigation and the series includes all those operated on as emer-

TABLE I
SITE OF ULCER, SEX, AND YEAR OF PARTIAL GASTRECTOMY

| Site | Males | | | | | | | Females | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1948 | 1949 | 1950 | 1951 | 1952 | 1953 (½) | Total (%) | 1948 | 1949 | 1950 | 1951 | 1952 | 1953 (½) | Total (%) |
| Gastric | 42 | 46 | 39 | 41 | 49 | 23 | 240 (30·9) | 8 | 19 | 11 | 12 | 19 | 10 | 79 (43·3) |
| Duodenal | 47 | 102 | 87 | 94 | 85 | 36 | 451 (58·4) | 9 | 15 | 16 | 25 | 22 | 3 | 90 (49·2) |
| Gastric plus duodenal | 5 | 6 | 14 | 7 | 11 | 4 | 47 (6·1) | 4 | — | 3 | 1 | 3 | — | 11 (6·0) |
| Other sites* | 2 | 4 | 13 | 7 | 4 | 4 | 34 (4·5) | 1 | — | — | — | 2 | — | 3 (1·6) |
| Total | 96 | 158 | 153 | 149 | 149 | 67 | 772 | 22 | 34 | 30 | 38 | 46 | 13 | 183 |

*Other sites includes stomal ulcer after gastroenterostomy and prolapse of gastric mucous membrane through pyloric ring.

TABLE II
AGE AT TIME OF PARTIAL GASTRECTOMY

| Age in Years | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | All Sites | Gastric | Duodenal | All Sites | Gastric | Duodenal |
| | No. | No. | No. | No. | No. | No. |
| Under 25 | 14 (0·8%) | — | 12 (2·7%) | 3 (1·6%) | 1 (1·3%) | 2 (2·2%) |
| 25-34 | 80 (10·3%) | 9 (3·8%) | 64 (14·2%) | 20 (10·9%) | 8 (10·1%) | 12 (13·3%) |
| 35-44 | 186 (24·1%) | 54 (22·6%) | 115 (25·5%) | 39 (21·3%) | 10 (12·7%) | 27 (30·0%) |
| 45-54 | 289 (37·5%) | 96 (39·7%) | 164 (36·3%) | 54 (29·5%) | 22 (27·8%) | 28 (31·1%) |
| 55-64 | 159 (20·6%) | 63 (26·4%) | 77 (17·1%) | 53 (29·0%) | 30 (38·0%) | 19 (21·1%) |
| 65 and over | 44 (5·7%) | 18 (7·5%) | 19 (4·2%) | 14 (7·7%) | 8 (10·1%) | 2 (2·2%) |
| Total | 772 | 240 | 451 | 183 | 79 | 90 |

N.B.—In this table the group with both gastric and duodenal ulcer and the group classed as "other sites" are not analysed because they are relatively small.

gencies, the majority of the latter having been operated on for haematemesis or melaena.

The number of patients considered in this review is 955 and the distribution of these according to sex, age, and site of ulcer, is shown in Tables I and II.

In duodenal ulcer the average age for men was 45·9 years and for women 45·8 years, while in gastric ulcer it was 50·6 years for men and 51·6 years for women.

The proportion of duodenal to gastric ulcer is 1 . 7 : 1, the percentage of gastric ulcers in this series being rather higher than in most other series.

### Cases Followed Up

Of the total of 955 patients, 79 were known to be dead at the time of the follow-up investigation and of the remaining 876 the number available for assessment by us was 826 (94·3%) (Table III). Some of the patients not traced and also some of those who had died some considerable time after operation had been seen at some time previously in the routine follow-up clinic and some assessment of the results of their operations had been made. Where this is appropriate such information will be given in this paper.

Table IV

MORTALITY RATES ACCORDING TO AGE

| Age (years) | Total Cases | Died | Mortality Rate % |
|---|---|---|---|
| Under 44 | 342 | 5 | 1·46 |
| 45-54 | 343 | 10 | 2·92 |
| 55-64 | 212 | 14 | 6·6 |
| Over 65 | 58 | 8 | 13·8 |

Table III

DEATHS AND NUMBERS OF CASES FOLLOWED UP ACCORDING TO SEX AND SITE OF ULCER

| | Total Operated | Operation Deaths | Late Gastrectomy | Pulmonary Tuberculosis | Other Diseases and Accidents | Total Deaths | Not Followed Up | Followed Up |
|---|---|---|---|---|---|---|---|---|
| Duodenal ulcer (men) | 451 | 16 (3·5%) | 2 | 0 | 9 | 27 | 21 (4·7%) | 403 |
| Duodenal ulcer (women) | 90 | 2 (2·2%) | 0 | 0 | 1 | 3 | 5 (5·6%) | 82 |
| Gastric ulcer (men) | 240 | 9 (3·8%) | 1 | 7 | 10 | 27 | 14 (5·8%) | 199 |
| Gastric ulcer (women) | 79 | 3 (3·8%) | 0 | 1 | 7 | 11 | 3 (3·8%) | 65 |
| Duodenal and gastric ulcer (men) | 47 | 3 (6·4%) | 2 | 0 | 1 | 6 | 4 (8·6%) | 37 |
| Duodenal and gastric ulcer (women) | 11 | 0 (0%) | 0 | 0 | 0 | 0 | 1 (9·1%) | 10 |
| Others (men) | 34 | 4 (11·8%) | 0 | 0 | 1 | 5 | 2 (5·9%) | 27 |
| Others (women) | 3 | 0 (0%) | 0 | 0 | 0 | 0 | 0 (0%) | 3 |
| Total (men) | 772 | 32 (4·1%) | 5 | 7 | 21 | 65 | 41 (5·3%) | 666 |
| Total (women) | 183 | 5 (2·7%) | 0 | 1 | 8 | 14 | 9 (4·9%) | 160 |
| Grand total | 955 | 37 (3·9%) | 5 | 8 | 29 | 79 | 50 (5·2%) | 826 |

### Deaths

Of the 79 patients known to be dead, 37 could be classified in the group "operative mortality", while a further five were styled "late gastrectomy deaths" since they died of late complications attributable to partial gastrectomy. Eight patients died of pulmonary tuberculosis which we considered was probably related to the gastrectomy (Thorn *et al.*, 1956). The remaining 29 died of other diseases unassociated with the operation.

The operative mortality rate, which included all patients who died before making a complete recovery from operation, was 3·87%, but it showed a considerable variation according to age (Table IV).

While deaths due to technical failures (10 cases, 1·05%) were spread evenly over all age groups, those due to cardiovascular (nine cases, 0·84%) and respiratory causes (10 cases, 1·05%) accounted for the great increase in mortality in the older patients.

### Assessment of the Results of Gastrectomy

In the investigation carried out by two of us (B and T) many aspects of the result of gastrectomy were considered. These included the relative amounts of work lost per year before and after operation, earning capacity, change of occupation, post-gastrectomy symptoms, bowel habits following gastrectomy, pre- and post-operative body weights and their comparison with standard weights, evidence of gastrointestinal haemorrhage before and after operation, post-operative anaemia (including haemoglobin estimation at our interview), and chest radiograph. A final assessment, in which the patient's own assessment of his or her condition was taken into account, was made of the result of the operation in each case seen. Where opinions conflicted the lower or poorer estimate of the result is the one given.

We assessed results according to five basic groups. These, over all, were similar to the groups or grades used by Visick (1948a), but we adapted them slightly so that the patients, in making their own assessment, could clearly decide which group they considered they were in.

These five groups were as follows:—

GROUP 1.—Completely symptom-free and able to lead a normal life.

GROUP 2.—Mild symptoms needing no dietary care or any other treatment and not interfering with normal life.

GROUP 3.—Mild symptoms which need dietary care or other treatment but not sufficient to interfere with normal life.

GROUP 4.—Symptoms, which, or the care of which, interfere with normal life but where the patient on the whole is better than he was before operation.

GROUP 5.—Symptoms as a result of which the patient is neither better nor worse than before operation.

In order to obtain groups large enough to give figures of statistical significance, we have added groups 1 and 2 together and called them "satisfactory results" and groups 4 and 5 together and called them "unsatisfactory results".

In all instances the assessment given is that of the original gastrectomy. In some cases subsequent operations have been performed, for example, refashioning of gastrectomy, vagotomy, enteroanastomosis, which have relieved the patient of his or her post-gastrectomy symptoms and have correspondingly improved the result. Such cases, in our review of the original operation, are still classified in group 5. Symptoms or the necessity for medical treatment suggesting a recurrent ulcer, even where no further surgery has been done and even if the patient's condition is satisfactory on such a medical régime, have similarly been placed in group 5. On this basis 826 cases have been classified according to sex and ulcer site and the results are given in Table V. Over all we may say that the 540 patients in groups 1 and 2 (65·4% of the cases followed up) were satisfactory, and needed no further treatment, and that the 727 in groups 1, 2, and 3 (88%) were able to lead a more normal life after the operation than beforehand. The remaining 99 patients, *i.e.*, groups 4 and 5, were unable to lead a normal life after the operation, and of these 6·9%, *i.e.*, group 5 patients, were not improved at all or were even worse than before operation.

FACTORS INFLUENCING RESULT.—In discussing these cases we have tried to determine if there was any significant factor or factors which influenced the result. We therefore present analyses in such a way that any such factors may become apparent. Although in most instances we have analysed and assessed all five groups of results individually, we shall compare two main groups: (*a*) the satisfactory results (groups 1 and 2) and (*b*) the unsatisfactory results (groups 4 and 5) and only where it may seem significant will the analyses of all five groups be given separately. Furthermore, in an attempt to obtain fairly large groups of similar cases we have taken four main sub-groups: (i) Male duodenal ulcer, (ii) female duodenal ulcer, (iii) male gastric ulcer, and (iv) female gastric ulcer. Other groups were so small when broken down that their numbers were of no significance when trying to determine causative factors.

TABLE V
RESULTS OF GASTRECTOMY

| | Group | | | | | Total |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| Duodenal ulcer (men) | 119 (29·5%) | 158 (39·2%) | 74 (18·4%) | 17 (4·2%) | 35 (8·7%) | 403 |
| Duodenal ulcer (women) | 17 (20·7%) | 30 (36·6%) | 27 (32·9%) | 3 (3·7%) | 5 (6·1%) | 82 |
| Gastric ulcer (men) | 63 (31·7%) | 71 (35·7%) | 42 (21·1%) | 13 (6·5%) | 10 (5·0%) | 199 |
| Gastric ulcer (women) | 15 (23·1%) | 22 (33·8%) | 21 (32·3%) | 5 (7·7%) | 2 (3·1%) | 65 |
| Duodenal and gastric ulcer (men) | 10 (27·0%) | 13 (35·1%) | 11 (29·7%) | 1 (2·7%) | 2 (5·4%) | 37 |
| Duodenal and gastric ulcer (women) | 1 (10·0%) | 2 (20·0%) | 5 (50·0%) | 2 (20·0%) | 0 (0%) | 10 |
| Others (men) | 6 (22·2%) | 11 (40·7%) | 6 (22·2%) | 1 (3·7%) | 3 (11·1%) | 27 |
| Others (women) | 2 (66·7%) | 0 (0%) | 1 (33·3%) | 0 (0%) | 0 (0%) | 3 |
| Total (men) | 198 (29·7%) | 253 (38·0%) | 133 (20·0%) | 32 (4·8%) | 50 (7·5%) | 666 |
| Total (women) | 35 (21·9%) | 54 (33·8%) | 54 (33·8%) | 10 (6·3%) | 7 (4·4%) | 160 |
| Grand total | 233 (28·2%) | 307 (37·2%) | 187 (22·6%) | 42 (5·1%) | 57 (6·9%) | 826 |

(1) *Effect of Length of Follow-up on Result of Gastrectomy.*—The results of operation in the four main sub-groups mentioned in the last paragraph were assessed against length of follow-up. Since the operations had been performed over a number of years the follow-up time varied from one to six years.

In the analyses the percentage of good results in the total of all the four sub-groups showed a progressive fall during the first four years after operation, but following this the percentages rose again. In the larger sub-groups the same trend is reflected, while in the smaller ones the figures were too small to be significant.

The probable explanation for this peculiar variation in the results is that while some causes of failure, such as recurrent ulcer, might slowly increase with time, other forms of post-gastrectomy symptoms, which may adversely affect the result, sometimes diminish with the passage of time. From the records available at the previous follow-up clinic it was apparent that 12 patients whom we saw and assessed as satisfactory had had, at some time previously, symptoms which would have made them unsatisfactory if we had seen them at that time. On the other hand nine patients whom we classed as unsatisfactory had been quite well for some considerable time (four cases for as long as four years) before deteriorating. This possible variation in the result from time to time illustrates the difficulty of assessing results against length of follow-up, and Visick (1948b) has also drawn attention to it.

However, since there is no particular trend for results to move gradually from group 1 to group 5 or vice versa, and also since the percentage results for each year group did not show any great variation from the average result for the total, we shall not, having pointed out these facts, subdivide the cases according to length of follow-up in our evaluations of other factors.

(2) *Effect of Age on Result of Gastrectomy.*—There appears to be no significant difference in the results between the various age groups (Table VI) and in this series we conclude that age does not affect the result of gastrectomy.

(3) *Effect of Site of Ulcer and of Sex on Results of Gastrectomy.*—In an effort to determine whether sex or the original site of the ulcer affects the result of the gastrectomy, we have condensed the totals shown in Table VII from the previous results given.

As far as the satisfactory results are concerned there appears to be no difference between gastric and duodenal ulcer in either sex and this is reflected in the totals. There is a difference in the results, however, between male and female which is significant ($P>0{\cdot}02$) in the total series and is just significant for duodenal ulcer alone. In the cases with unsatisfactory results there appears to be no significant difference either in sex or in the site of ulcer. We may therefore conclude that the original site of the ulcer, *e.g.*, gastric or duodenal, does not appear to affect the result of gastrectomy. As far as the sex is concerned, male patients appear to do better than female patients to a degree that is just statistically significant.

TABLE VI

RESULTS OF GASTRECTOMY ACCORDING TO AGE

| | Age | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Results (Followed Up) | | | Dead and Not Followed Up | Total | Results (Followed Up) | | | Dead and Not Followed Up | Total |
| | | Groups 1 and 2 | Group 3 | Groups 4 and 5 | | | Groups 1 and 2 | Group 3 | Groups 4 and 5 | | |
| Gastric ulcer | Under 44 | 45 (76%) | 8 | 6 (10·2%) | 4 | 63 | 12 (80%) | — | 3 (20%) | 4 | 19 |
| | 45-54 | 52 (61%) | 22 | 9 (10·8%) | 13 | 96 | 8 (38%) | 11 | 2 (9·5%) | 1 | 22 |
| | 55-64 | 31 (64%) | 9 | 8 (17%) | 15 | 63 | 15 (60%) | 8 | 2 (8%) | 5 | 30 |
| | 65 + | 6 (67%) | 3 | — | 9 | 18 | 3 (75%) | 1 | — | 4 | 8 |
| Total | | 134 (67%) | 42 | 23 (12%) | 41 | 240 | 38 (58%) | 20 | 7 (11%) | 14 | 79 |
| Duodenal ulcer | Under 44 | 119 (68%) | 33 | 23 (12%) | 16 | 191 | 21 (55%) | 12 | 5 (13%) | 3 | 41 |
| | 45-54 | 97 (66%) | 24 | 25 (17%) | 18 | 164 | 16 (59%) | 10 | 1 (4%) | 1 | 28 |
| | 55-64 | 50 (74%) | 14 | 4 (5·8%) | 9 | 77 | 9 (60%) | 5 | 1 (7%) | 4 | 19 |
| | 65 + | 11 (79%) | 3 | — | 5 | 19 | 1 (50%) | — | 1 (50%) | — | 2 |
| Total | | 277 (69%) | 74 | 52 (13%) | 48 | 451 | 47 (57%) | 27 | 8 (9·7%) | 8 | 90 |

TABLE VII

EFFECTS OF SEX AND SITE OF ULCER ON RESULT OF OPERATION

| | "Satisfactory" Results | | | "Unsatisfactory" Results | | |
|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total |
| Gastric ulcer | 134/199 = 67·3% | 38/65 = 58·5% | 172/264 = 65·15% | 23/199 | 7/65 | 30/264 = 11·4% |
| Duodenal ulcer | 277/403 = 68·7% | 47/82 = 57·3% | 324/485 = 66·80% | 52/403 | 8/82 | 60/485 = 12·4% |
| Total | 411/602 = 68·27% | 85/147 = 57·82% | | 75/602 = 12·5% | 15/147 = 10·2% | |

(4) *Duration of Symptoms before Gastrectomy and Effect on Result of Operation.*—It had previously been our impression in the Professorial Unit follow-up clinic that the longer the duration of symptoms before gastrectomy the better were the results of the operation, particularly in cases of duodenal ulcer. We therefore analysed the results according to the length of symptoms before operation and these figures are represented in Fig. 1.

It will be seen from this graph, however, that there appears to be no statistical trend to support this view and we conclude that the duration of symptoms before operation does not appear to alter the results materially.

(5) *Effect of Type of Operation on Result of Gastrectomy.*—In the total series the operations were performed by a number of surgeons and no particular scheme of operations was undertaken.

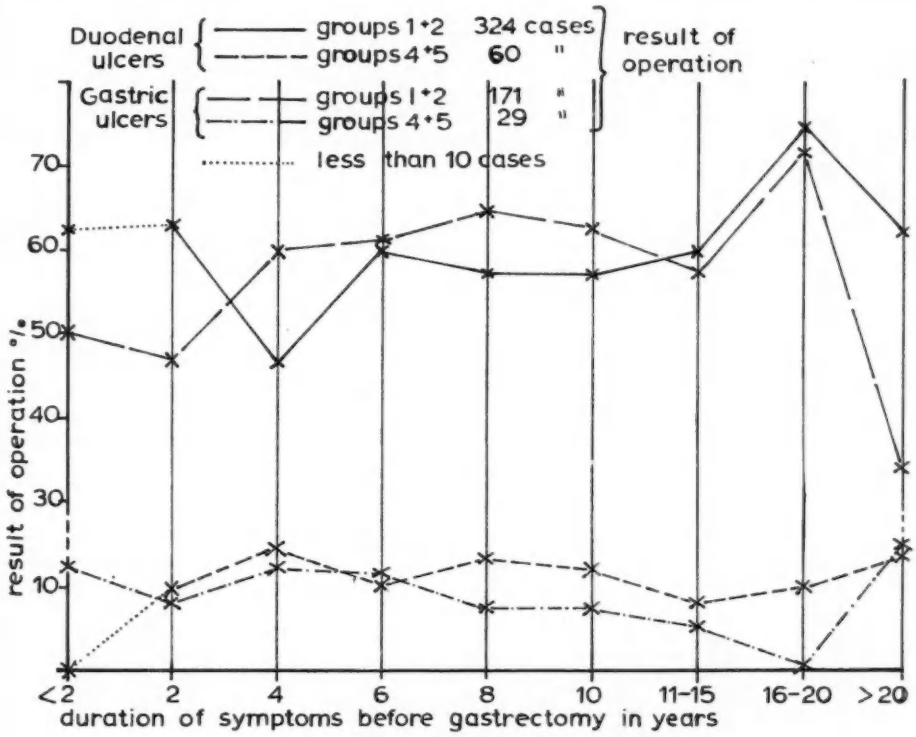


FIG. 1.—*Duration of symptoms related to results of gastrectomy.*

Originally the Polya operation was the standard one and 828 gastrectomies of this type were done. The antecolic operation with the afferent loop to the lesser curvature of the stomach was the operation of choice (725 cases) and of these the Hofmeister variation was performed in 235 cases. A limited number of retrocolic operations was performed rather sporadically (103 cases), 39 of which were of the Hofmeister type. Later a number of Billroth 1 gastrectomies were carried out, a total of 127 of this operation being included in this series. The amount of stomach removed varied from 50% to 90% throughout all types of operation.

We have carried out analyses to determine if any particular type of operation affected the overall result. We are not assessing only recurrent ulcer rates but all factors influencing the final result of the cases.

The following main comparisons have been made: (i) Polya gastrectomy versus Billroth; (ii) antecolic versus retrocolic Polya; (iii) Polya versus Polya Hofmeister; (iv) a more limited resection of stomach (two-thirds or less) versus a more extensive resection (more than two-thirds). The results are shown in Tables VIII, IX, and X.

After comparing not only percentages but also the total numbers of cases in each group, we have concluded from these figures as follows:—

(*a*) For gastric ulcer the Billroth operation gives significantly better results than the Polya operation for the total series, and for men alone. In women the difference is not statistically significant but this is probably because the total number of cases is relatively small.

(*b*) For duodenal ulcer there does not appear to be any significant difference in the results between Polya and Billroth operation.

(*c*) The extent of gastric resection did not appear to affect significantly the results in either the Billroth or the Polya operations performed for gastric ulcer.

(*d*) Similarly the amount of stomach removed did not appear to affect the results of Billroth gastrectomy for duodenal ulcer, nor the results of Polya gastrectomy for this condition in the total series. In men alone, however, the more limited resections (two-thirds or less) in the Polya operations for duodenal ulcer were significantly better than the more extensive resections.

(*e*) The number of cases of retrocolic Polya operation is relatively too small as compared with the antecolic ones to make the percentages of results significant. Only in duodenal ulcers in women does there appear to be a really significant difference and here the antecolic operation appears to be the better one.

(*f*) The Polya Hofmeister operation does not appear to give better results for duodenal ulcer

TABLE VIII

COMPARISON OF POLYA AND BILLROTH OPERATIONS

| Type of Ulcer | Type of Operation | Extent of Resection | Results | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Male | | | Female | | | Total | | |
| | | | No. Followed | Groups 1 and 2 | Groups 4 and 5 | No. Followed | Groups 1 and 2 | Groups 4 and 5 | No. Followed | Groups 1 and 2 | Groups 4 and 5 |
| Gastric | Polya | Two-thirds or less | 99 | 63 (63·6) | 5 | 22 | 14 (63·6) | 3 | 121 | 77 (63·6) | 8 |
| | | Over two-thirds | 55 | 30 (54·5) | 17 | 22 | 9 (40·9) | 4 | 77 | 39 (50·6) | 21 |
| | | Total of all cases | 154 | 93 (60·4) | 22 | 44 | 23 (52·3) | 7 | 198 | 116 (58·6) | 29 |
| | Billroth | Two-thirds or less | 40 | 37 (92·5) | 1 | 16 | 11 (68·7) | 0 | 56 | 48 (85·7) | 1 |
| | | Over two-thirds | 5 | 4 | 0 | 5 | 3 | 0 | 10 | 7 (70·0) | 0 |
| | | Total of all cases | 45 | 41 (91·1) | 1 | 21 | 14 (66·7) | 0 | 66 | 55 (83·3) | 1 |
| | Total (Polya and Bilroth) | Two-thirds or less | 139 | 100 (71·9) | 6 | 38 | 25 (65·8) | 3 | 177 | 125 (78·5) | 9 |
| | | Over two-thirds | 60 | 34 (56·7) | 17 | 27 | 12 (44·4) | 4 | 87 | 46 (52·9) | 21 |
| | | Total of all cases | 199 | 134 (67·3) | 23 | 65 | 37 (56·9) | 7 | 264 | 171 (64·8) | 30 |
| Duodenal | Polya | Two-thirds or less | 277 | 197 (71·1)) | 32 | 61 | 35 (57·4) | 5 | 338 | 232 (68·6) | 37 |
| | | Over two-thirds | 92 | 56 (60·9) | 16 | 15 | 8 (53·3) | 3 | 107 | 64 (59·8) | 19 |
| | | Total of all cases | 369 | 253 (68·6) | 48 | 76 | 43 (56·6) | 8 | 445 | 296 (66·5) | 56 |
| | Billroth | Two-thirds or less | 26 | 17 (65·4) | 4 | 6 | 4 | 0 | 32 | 21 (65·6) | 4 |
| | | Over two-thirds | 8 | 7 (87·5) | 0 | 0 | 0 | 0 | 8 | 7 (87·5) | 0 |
| | | Total of all cases | 34 | 24 (70·6) | 4 | 6 | 4 | 0 | 40 | 28 (70·0) | 4 |
| | Total (Polya and Billroth) | Two-thirds or less | 303 | 214 (70·6) | 36 | 67 | 39 (58·2) | 5 | 370 | 253 (68·4) | 41 |
| | | Over two-thirds | 100 | 63 (63·0) | 16 | 15 | 8 (53·3) | 3 | 115 | 71 (61·7) | 19 |
| | | Total of all cases | 403 | 277 (68·7) | 52 | 82 | 47 (57·3) | 8 | 485 | 324 (66·8) | 60 |
| Total | Polya | Two-thirds or less | 376 | 260 (69·1) | 37 | 83 | 49 (59·0) | 8 | 459 | 309 (67·3) | 45 |
| | | Over two-thirds | 147 | 86 (58·5) | 33 | 37 | 17 (45·9) | 7 | 184 | 103 (56·0) | 40 |
| | | Total of all cases | 523 | 346 (66·2) | 70 | 120 | 66 (55·0) | 15 | 643 | 412 (64·1) | 85 |
| | Billroth | Two-thirds or less | 66 | 54 (81·8) | 5 | 22 | 15 (68·2) | 0 | 88 | 69 (78·4) | 5 |
| | | Over two-thirds | 13 | 11 (84·6) | 0 | 5 | 3 (60·0) | 0 | 18 | 14 (77·8) | 0 |
| | | Total of all cases | 79 | 65 (82·3) | 5 | 27 | 18 (66·7) | 0 | 106 | 83 (78·3) | 5 |
| | Total (Polya and Billroth) | Two-thirds or less | 442 | 314 (71·0) | 42 | 105 | 64 (61·0) | 8 | 547 | 378 (69·1) | 50 |
| | | Over two-thirds | 160 | 97 (60·6) | 33 | 42 | 20 (47·6) | 7 | 202 | 117 (57·9) | 40 |
| | | Total of all cases | 602 | 411 (68·3) | 75 | 147 | 84 (57·1) | 15 | 749 | 495 (66·1) | 90 |

Percentages of groups 1 and 2 results are shown in parentheses.

TABLE IX

COMPARISON OF ANTECOLIC AND RETROCOLIC POLYA OPERATIONS

| Type of Ulcer | Type of Operation | Extent of Resection | Results | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Male | | | Female | | | Total | | |
| | | | No. Followed | Groups 1 and 2 | Groups 4 and 5 | No. Followed | Groups 1 and 2 | Groups 4 and 5 | No. Followed | Groups 1 and 2 | Groups 4 and 5 |
| Gastric | Antecolic Polya | Two-thirds or less | 87 | 54 (62·1) | 5 | 20 | 12 (60·0) | 3 | 107 | 66 (61·7) | 8 |
| | | Over two-thirds | 48 | 24 (50·0) | 16 | 17 | 7 (41·2) | 3 | 65 | 31 (47·5) | 19 |
| | | Total of all cases | 135 | 78 (57·8) | 21 | 37 | 19 (51·4) | 6 | 172 | 97 (56·4) | 27 |
| | Retrocolic Polya | Two-thirds or less | 12 | 9 (75·0) | 0 | 2 | 2 | 0 | 14 | 11 (78·6) | 0 |
| | | Over two-thirds | 7 | 6 | 1 | 5 | 2 | 1 | 12 | 8 (66·7) | 2 |
| | | Total of all cases | 19 | 15 (78·9) | 1 | 7 | 4 | 1 | 26 | 19 (73·1) | 2 |
| Duodenal | Antecolic Polya | Two-thirds or less | 245 | 175 (71·4) | 29 | 54 | 32 | 5 | 299 | 207 (69·2) | 34 |
| | | Over two-thirds | 77 | 45 (58·4) | 14 | 13 | 8 (61·5) | 2 | 90 | 53 (58·9) | 16 |
| | | Total of all cases | 322 | 220 (68·3) | 43 | 67 | 40 (59·7) | 7 | 389 | 260 (66·8) | 50 |
| | Retrocolic Polya | Two-thirds or less | 32 | 22 (68·8) | 3 | 7 | 3 (42·9) | 0 | 39 | 25 (64·1) | 3 |
| | | Over two-thirds | 15 | 11 (73·3) | 2 | 2 | 0 | 1 | 17 | 11 (64·7) | 3 |
| | | Total of all cases | 47 | 33 (70·2) | 5 | 9 | 3 (33·3) | 1 | 56 | 36 (64·3) | 6 |
| Total | Antecolic Polya | Two-thirds or less | 332 | 229 (69·0) | 34 | 74 | 44 (59·5) | 8 | 406 | 273 (67·2) | 42 |
| | | Over two-thirds | 125 | 69 (55·2) | 30 | 30 | 15 (50·0) | 5 | 155 | 84 (54·2) | 35 |
| | | Total of all cases | 457 | 298 (65·2) | 64 | 104 | 59 (56·7) | 13 | 561 | 357 (63·6) | 77 |
| | Retrocolic Polya | Two-thirds or less | 44 | 31 (70·5) | 3 | 9 | 5 | 0 | 53 | 36 (67·9) | 3 |
| | | Over two-thirds | 22 | 17 (77·3) | 3 | 7 | 2 | 2 | 29 | 19 (65·5) | 5 |
| | | Total of all cases | 66 | 48 (72·7) | 6 | 16 | 7 | 2 | 82 | 55 (67·1) | 8 |

Percentages of groups 1 and 2 results are shown in parentheses. Totals of Polya operations are given in Table VIII.

TABLE X

COMPARISON OF POLYA AND POLYA HOFMEISTER OPERATIONS

| Type of Ulcer | Type of Operation | Extent of Resection | Results | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Male | | | Female | | | Total | | |
| | | | No. Followed | Groups 1 and 2 | Groups 4 and 5 | No. Followed | Groups 1 and 2 | Groups 4 and 5 | No. Followed | Groups 1 and 2 | Groups 4 and 5 |
| Gastric | Polya | Two-thirds or less | 71 | 46 (64·8) | 4 | 11 | 4 (36·4) | 3 | 82 | 50 (61·0) | 7 |
| | | Over two-thirds | 40 | 22 (55·0) | 11 | 19 | 7 (36·8) | 3 | 59 | 29 (49·2) | 14 |
| | | Total of all cases | 111 | 68 (61·3) | 15 | 30 | 11 (36·7) | 6 | 141 | 79 (56·0) | 21 |
| | Polya Hofmeister | Two-thirds or less | 28 | 17 (60·7) | 1 | 11 | 10 (90·9) | 0 | 39 | 27 (69·2) | 1 |
| | | Over two-thirds | 15 | 8 (53·3) | 6 | 3 | 2 | 1 | 18 | 10 (55·5) | 7 |
| | | Total of all cases | 43 | 25 (58·1) | 7 | 14 | 12 (85·7) | 1 | 57 | 37 (64·9) | 8 |
| Duodenal | Polya | Two-thirds or less | 174 | 123 (70·7) | 18 | 43 | 22 (51·2) | 4 | 217 | 145 (66·8) | 22 |
| | | Over two-thirds | 63 | 39 (61·9) | 9 | 12 | 7 (58·3) | 3 | 75 | 46 (61·3) | 12 |
| | | Total of all cases | 237 | 162 (68·4) | 27 | 55 | 29 (52·7) | 7 | 292 | 191 (65·4) | 34 |
| | Polya Hofmeister | Two-thirds or less | 103 | 74 (71·8) | 14 | 18 | 13 (72·2) | 1 | 121 | 87 (71·9) | 15 |
| | | Over two-thirds | 29 | 17 (58·6) | 7 | 3 | 1 | 0 | 32 | 18 (56·3) | 7 |
| | | Total of all cases | 132 | 91 (68·9) | 21 | 21 | 14 (66·7) | 1 | 153 | 105 (68·6) | 22 |
| Total | Polya | Two-thirds or less | 245 | 169 (69·0) | 22 | 54 | 26 (48·1) | 7 | 299 | 195 (65·2) | 29 |
| | | Over two-thirds | 103 | 61 (59·2) | 20 | 31 | 14 (45·2) | 6 | 134 | 75 (56·0) | 26 |
| | | Total of all cases | 348 | 230 (66·1) | 42 | 85 | 40 (47·1) | 13 | 433 | 270 (62·4) | 55 |
| | Polya Hofmeister | Two-thirds or less | 131 | 91 (69·5) | 15 | 29 | 23 (79·3) | 1 | 160 | 114 (71·3) | 16 |
| | | Over two-thirds | 44 | 25 (56·8) | 13 | 6 | 3 | 1 | 50 | 28 (56·0) | 14 |
| | | Total of all cases | 175 | 116 (66·3) | 28 | 35 | 26 (74·3) | 2 | 210 | 142 (67·6) | 30 |

Percentages of groups 1 and 2 results are shown in parentheses. Totals of Polya operations are given in Table VIII.

than the original Polya operation and there is similarly no difference in the total number done for gastric ulcer. For gastric ulcer in women alone, however, the Polya Hofmeister operation is significantly better than the Polya operation.

(6) *Indications for Gastrectomy and their Effect on Results.*—From the notes made at the time of the original operation we have classified the indications for the operation. We considered 10 primary indications for gastrectomy but in some cases two or more of these indications may have been present. In Table XI we show an analysis of the results of operations for duodenal ulcer and gastric ulcer in comparison with nine primary indications. (The tenth indication was stomal ulcer after previous gastroenterostomy and this, of course, does not apply in these two conditions.) Where two or more indications have been present we have taken the more serious one as the primary one. In addition to its interest as an analysis of the indications for gastrectomy, the table shows that results of gastrectomy do not appear to be related in any significant way to the indication for the operation.

Of the 955 patients in the total series, 360 had suffered a complication of their ulcer, such as stenosis, bleeding, perforation, etc. In the

TABLE XI

INDICATIONS FOR GASTRECTOMY AND THEIR EFFECT ON RESULT OF OPERATION

| | Primary Indication for Gastrectomy | Duodenal Ulcers—Results | | | | Gastric Ulcers—Results | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Groups 1 and 2 | Groups 3 | Groups 4 and 5 | Total Followed Up | Groups 1 and 2 | Group 3 | Groups 4 and 5 | Total Followed Up |
| Male | Pain (indigestion etc.) | 176 (67·2) | 52 (19·8) | 34 (13) | 262 | 88 (65·7) | 30 (22·4) | 16 (11) | 134 |
| | Pain, etc., plus previous perforation | 24 (72·7) | 6 (18·2) | 3 (9·1) | 33 | 6 (100) | — | — | 6 |
| | Repeated previous haemorrhages | 25 (78·1) | 3 (9·4) | 4 (12·5) | 32 | 5 (62·5) | 3 (27·5) | — | 8 |
| | Haemorrhage at time of operation (acute ulcer) | — | — | 1 | 1 | 1 | 1 | 1 | 3 |
| | Haemorrhage at time of operation (chronic ulcer) | 14 (73·7) | 3 (15·8) | 2 (10·5) | 19 | 10 (71·4) | 2 (14·3) | 2 (14·3) | 14 |
| | Pyloric stenosis | 38 (73·1) | 8 (15·4) | 6 (11·5) | 52 | 9 (81·8) | 1 (9·1) | 1 (9·1) | 11 |
| | Hour-glass obstruction | — | — | — | — | 1 | — | — | 1 |
| | Fear of malignancy | — | — | — | — | 14 (63·6) | 5 (22·7) | 3 (13·6) | 22 |
| | Original ulcer still active plus gastro-enterostomy | — | 2 | 2 | 4 | — | — | — | — |
| Female | Pain (indigestion, etc.) | 25 (50) | 19 (38) | 6 (12) | 50 | 22 (53·7) | 13 (31·7) | 6 (14·6) | 41 |
| | Pain, etc., plus previous perforation | 3 (75) | 1 | — | 4 | 1 | 1 | — | 2 |
| | Repeated previous haemorrhages | — | — | 2 | 2 | 1 | 1 | — | 2 |
| | Haemorrhage at time of operation (acute ulcer) | — | — | — | — | 1 | — | — | 1 |
| | Haemorrhage at time of operation (chronic ulcer) | 2 | 1 | — | 3 | 3 | 1 | 1 | 5 |
| | Pyloric stenosis | 17 (81) | 4 (19) | — | 21 | 5 | — | — | 5 |
| | Hour-glass obstruction | — | — | — | — | 1 | 1 | — | 2 |
| | Fear of malignancy | — | 2 | — | 2 | 4 | 3 | — | 7 |
| | Original ulcer still active plus gastro-enterostomy | — | — | — | — | — | — | — | — |

Actual number of cases followed up in each group is given. Percentages are given in parentheses except where number of cases is very small.

772 men there were 287 such cases (37·1%) and in the 183 women 73 cases (39·8%). Altogether 11·8% of the total had pyloric stenosis, 8·6% had previously had a perforation, 7·7% had had previous repeated haemorrhages, and a further 6% were operated on as emergencies for haemorrhage.

### OTHER FACTORS INFLUENCED BY GASTRECTOMY

It has been pointed out that the "result" discussed so far is the overall result of operation. The influence of gastrectomy on some other factors will now be analysed.

EARNING CAPACITY AFTER GASTRECTOMY.—We have compared the earning capacity of each patient before and after operation as far as possible. Earning capacity rather than actual earning was taken, since in quite a number of cases wages or salaries have been affected by other factors unconnected with gastrectomy. In such instances, although the actual earnings have changed, we have specified earning capacity as "no change". In some patients, particularly women, there was no paying occupation before or after operation and these have been excluded, so that the total number available for assessment in this group is 749. We have taken all ulcer, age, and sex groups together and have classified them according to the result of gastrectomy. Of the good results (groups 1 and 2), 39·3% showed an increase in earning capacity (11% having as much as a 50% increase), while only 3·2% showed a decrease. In the poor results (groups 4 and 5), 12·2% had an increased earning capacity while 37·8% showed a decrease and this deterioration was adjudged to be due to the operation result. Group 3 results, which had been assessed as not interfering with normal life, showed a 27·6% increase and only an 8% decrease in earning capacity which is considered to be a fair justification of the method of assessment.

AMOUNT OF TIME LOST FROM WORK AFTER GASTRECTOMY.—The same general principles as above were used to assess working time lost per year before and after gastrectomy. Time lost was only considered in relation to gastrectomy, and where loss was quite obviously not due to result of the operation the case has either been excluded or a corrected estimate has been given. The number of patients available for analysis is again 749, the same cases as used in the evaluation of earning capacity. The cases are again divided according to the results of gastrectomy (Table XII). It will be seen that there is a significant drop in the amount of time lost

TABLE XII

WORKING TIME LOST BEFORE AND AFTER GASTRECTOMY

| Result of Gastrectomy | | Time Loss in Weeks per Year | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | | Nil | Up to 2 Weeks | 2-4 Weeks | 4-8 Weeks | 8-12 Weeks | 12+ Weeks | |
| Groups 1 and 2 | Loss before operation | 159 (32·1) | 17 (3·4) | 30 (6·0) | 89 (17·9) | 73 (14·7) | 128 (25·8) | 496 |
| | Loss after operation | 469 (94·6) | 11 (2·2) | 5 (1·0) | 3 (0·6) | 3 (0·6) | 5 (1·0) | 496 |
| Group 3 | Loss before operation | 58 (35·6) | 9 (5·5) | 6 (3·7) | 23 (14·1) | 23 (14·1) | 44 (27·0) | 163 |
| | Loss after operation | 136 (83·4) | 10 (6·1) | 7 (4·3) | 2 (1·2) | 3 (1·8) | 5 (3·1) | 163 |
| Groups 4 and 5 | Loss before operation | 29 (32·2) | 3 (3·3) | 11 (12·2) | 13 (14·4) | 18 (20·0) | 16 (17·8) | 90 |
| | Loss after operation | 40 (44·4) | 7 (7·8) | 8 (8·9) | 10 (11·1) | 7 (7·8) | 18 (20·0) | 90 |
| Total followed up | Loss before operation | 246 (32·8) | 29 (3·9) | 47 (6·3) | 125 (16·7) | 114 (15·2) | 188 (25·1) | 749 |
| | Loss after operation | 645 (86·1) | 28 (3·7) | 20 (2·7) | 15 (2·0) | 13 (1·7) | 28 (3·7) | 749 |

Percentages are shown in parentheses.

rom work when the patient has a good result from the operation (groups 1 and 2), and that the same applies in the patients who only had a moderate result (group 3). The amount of time lost by patients in groups 4 and 5 was not greatly altered. The fall of earning capacity in these patients allied to no increase of time loss was usually due to change of occupation.

OCCUPATION BEFORE AND AFTER GASTRECTOMY.—Occupations were classified according to the five social status groups specified by the General Register Office. Changes after operation would therefore only become apparent if the patient moved from one broad social group to another. In groups 1 and 2, 88·9% and in group 3, 82·8% showed no change. In groups 4 and 5, 71·1% remained unchanged but 22·2% had moved down the occupation scale.

GASTRO-DUODENAL HAEMORRHAGE AND ANAEMIA.—The occurrence of gastrointestinal haemorrhage as shown by haematemesis, malaena, or the evidence of anaemia before operation in the 955 cases operated upon and after operation in the 826 cases followed up is shown in Table XIII.

The actual haemoglobin levels of patients at the time of admission for operation are shown in Table XIV. Some of these were admitted as emergencies with bleeding or came in with anaemia and would have been transfused before operation was actually undertaken. We estimated the haemoglobin levels in 771 of the 826 cases followed up and the results of these are also shown in Table XIV.

TABLE XIII

GASTROINTESTINAL HAEMORRHAGE BEFORE AND AFTER OPERATION

| | No Haemorrhage | Haematemesis with or without Melaena | Melaena | Anaemia | Total |
|---|---|---|---|---|---|
| Before operation | 694 (72·7) | 172 (18·0) | 65 (6·8) | 24 (2·5) | 955 |
| After operation | 774 (93·7) | 6 (0·7) | 4 (0·5) | 42 (5·1) | 826 |

Percentages are shown in parentheses.
*The cases shown as "anaemia after operation" had needed treatment, and the anaemia had developed after the immediate period of the operation.

TABLE XIV

HAEMOGLOBIN LEVELS BEFORE AND AFTER OPERATION

| | | Levels of Haemoglobin as % of Normal | | | | | | | No. 4 with Known Haemoglobin | Not Known Haemoglobin | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean Level | 90+ | 80-89 | 70-79 | 60-69 | 50-59 | Under 50 | | | |
| Pre-operative | Male | 102·8 | 88·0 | 4·4 | 2·8 | 1·7 | 1·1 | 2·0 | 752 | 20 | 772 |
| | Female | 92·5 | 66·3 | 18·5 | 7·9 | 2·8 | 0·6 | 3·9 | 178 | 5 | 183 |
| Post-operative | Male | 94·3 | 71·0 | 16·5 | 7·8 | 3·5 | 1·0 | 0.2 | 624 | 42 | 666 |
| | Female | 86·6 | 49·6 | 22·5 | 14·3 | 6·1 | 5·5 | 2·0 | 147 | 13 | 160 |

*The number of cases where the haemoglobin level was known is given for men and women before and after operation. The figures given at each haemoglobin level are percentages of those totals.

The figures show a significant fall in the mean level of haemoglobin in both sexes after operation. Although the mean level in women is lower than in men both before and after operation, in this series the actual fall in men (8·5%) was greater than in women (5·9%).

BODY WEIGHT BEFORE AND AFTER GASTRECTOMY.—In all cases where we have sufficient information we have calculated the patient's actual body weight as a percentage above or below their standard body weight for age, height, and sex. The standard weights used are those given in the tables of Kemsley (1952). In Table XV we show these results for duodenal ulcer and for gastric ulcer cases in both sexes. To simplify the table we have expressed the number of cases in each instance as a percentage of the total, the latter being given in each group at the bottom of the table section. For instance, in the "best ever" weights for male duodenal ulcer cases, 42% of the total of 264 were at standard weight and this represents 111 patients. Each patient's weight had been noted on a number of occasions and these are interpreted as follows:—

(*a*) "*Best Ever*" *Weight.*—This is the highest the patient can remember attaining at any time before operation.

(*b*) *Weight just before Operation.*—This is the weight recorded in the patient's notes in hospital immediately before operation. (Since patients weighed at follow-up examinations were fully dressed, the weights have been suitably adjusted to be comparable.)

(*c*) *Weight One Year after Operation.*—These weights were available in most instances from the notes made at the routine gastrectomy follow-up clinic.

(*d*) *Weight at Time of Follow-up.*—These were the weights that we actually recorded in our investigation. The weights in this group include those of all cases however long the time since operation. Thus cases operated on as long ago as six years are included but also patients operated on only one year ago would also be represented.

We have taken the mean weight in duodenal ulcer and in gastric ulcer cases for both sexes and for both

TABLE XV

RESULT OF OPERATION AND WEIGHTS AT DIFFERENT TIMES

| Group | Result of Operation | Best Ever Weight | | | | Weight just before Operation | | | | Weight One Year after Operation | | | | Weight at Follow-up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Duodenal Ulcer | | Gastric Ulcer | | Duodenal Ulcer | | Gastric Ulcer | | Duodenal Ulcer | | Gastric Ulcer | | Duodenal Ulcer | | Gastric Ulcer | |
| | | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| 1 and 2 | Above ideal weight | | | | | | | | | | | | | | | | |
| | 20% or more | 11·8 | 22·7 | 5·5 | 9·0 | 4·9 | 6·6 | 0·8 | 2·9 | 3·1 | 7·3 | 1·6 | — | 5·2 | 8·9 | 1·6 | — |
| | 10% | 23·1 | 13·6 | 26·8 | 33·3 | 10·9 | 4·4 | 4·0 | 11·8 | 9·0 | 4·9 | 8·1 | 13·3 | 12·0 | 6·7 | 8·5 | 14·7 |
| | No difference | 42·0 | 18·2 | 39·4 | 12·2 | 32·7 | 22·2 | 25·4 | 11·8 | 27·5 | 12·2 | 29·8 | 16·7 | 26·6 | 11·1 | 31·0 | 23·5 |
| | Below ideal weight | | | | | | | | | | | | | | | | |
| | 10% | 20·1 | 25·0 | 24·4 | 27·3 | 33·1 | 13·3 | 46·1 | 11·8 | 37·3 | 22·0 | 39·5 | 23·3 | 26·7 | 24·4 | 38·0 | 17·6 |
| | 20% or more | 3·0 | 20·5 | 3·9 | 18·2 | 18·4 | 53·4 | 23·8 | 61·7 | 23·2 | 53·6 | 20·9 | 46·7 | 19·5 | 48·9 | 20·9 | 44·1 |
| | Mean weight | +2·3 | +0·5 | +0·7 | −0·9 | −4·9 | −12·9 | −9·2 | −14·7 | −6·9 | −12·2 | −7·2 | −12·0 | −5·4 | −10·9 | −7·1 | −10·6 |
| | Number of cases weight known | 264 | 44 | 127 | 33 | 266 | 45 | 126 | 34 | 255 | 41 | 124 | 30 | 267 | 45 | 129 | 34 |
| | Number of cases weight not known | 13 | 3 | 7 | 5 | 11 | 2 | 8 | 4 | 22 | 6 | 10 | 8 | 10 | 2 | 5 | 4 |
| 3 | Above ideal weight | | | | | | | | | | | | | | | | |
| | 20% or more | 9·6 | 14·8 | 4·8 | 10·0 | — | — | — | — | — | — | 2·5 | — | 1·4 | 3·7 | — | — |
| | 10% | 32·9 | 25·9 | 19·5 | 20·0 | 8·5 | — | 7·3 | — | 4·3 | 13·0 | 5·0 | — | 2·7 | 3·7 | 2·4 | — |
| | No difference | 35·6 | 18·5 | 36·6 | 25·0 | 36·6 | 15·4 | 17·1 | 10·0 | 27·1 | 4·3 | 5·0 | — | 24·3 | 14·8 | 12·2 | — |
| | Below ideal weight | | | | | | | | | | | | | | | | |
| | 10% | 20·5 | 25·9 | 34·1 | 20·0 | 42·3 | 26·9 | 29·3 | 35·0 | 42·9 | 26·1 | 40·0 | 31·6 | 50·0 | 18·5 | 29·3 | 30·0 |
| | 20% or more | 1·4 | 14·8 | 4·9 | 25·0 | 12·7 | 57·7 | 46·3 | 55·0 | 25·8 | 56·4 | 47·5 | 68·5 | 21·6 | 59·2 | 56·0 | 70·0 |
| | Mean weight | +2·9 | +1·1 | −0·7 | −3·0 | −6·2 | −15·8 | −12·2 | −18·0 | −9·3 | −15·7 | −13·5 | −21·1 | −9·2 | −13·7 | −14·6 | −20·5 |
| | Number of cases weight known | 73 | 27 | 41 | 20 | 71 | 26 | 41 | 20 | 70 | 23 | 40 | 19 | 74 | 27 | 41 | 20 |
| | Number of cases weight not known | 1 | — | 1 | — | 3 | 1 | 1 | — | 4 | 4 | 2 | 1 | — | — | 1 | — |
| 4 and 5 | Above ideal weight | | | | | | | | | | | | | | | | |
| | 20% or more | 6·0 | 14·3 | 5·0 | — | — | — | — | — | — | — | — | — | — | — | 4·5 | — |
| | 10% | 26·0 | 14·3 | 20·0 | 33·3 | 6·0 | 12·5 | 5·3 | — | 2·1 | — | — | — | 4·0 | — | — | — |
| | No difference | 52·0 | 42·9 | 40·0 | — | 40·0 | 37·5 | 36·8 | 16·7 | 29·2 | — | 5·3 | — | 22·0 | 14·3 | — | — |
| | Below ideal weight | | | | | | | | | | | | | | | | |
| | 10% | 10·0 | — | 25·0 | 33·3 | 36·0 | 25·0 | 26·3 | 16·7 | 37·5 | 25·0 | 31·6 | 40·0 | 48·0 | 14·3 | 27·3 | 16·7 |
| | 20% or more | 6·0 | 28·6 | 10·0 | 33·3 | 18·0 | 25·0 | 31·6 | 66·7 | 31·3 | 62·5 | 63·1 | 60·0 | 26·0 | 71·4 | 68·2 | 83·3 |
| | Mean weight | +1·6 | −1·4 | −1·5 | −6·7 | −1·7 | −7·5 | −8·9 | −1·5 | −9·8 | −21·3 | −16·8 | −18·0 | −9·8 | −15·7 | −17·7 | −23·3 |
| | Number of cases weight known | 50 | 7 | 20 | 6 | 50 | 8 | 19 | 6 | 48 | 8 | 19 | 5 | 50 | 7 | 22 | 6 |
| | Number of cases weight not known | 2 | 1 | 3 | 1 | 2 | — | 4 | 1 | 4 | — | 4 | 2 | 2 | 1 | 1 | 1 |

good (groups 1 and 2) and unsatisfactory (groups 4 and 5) operation results and represented them in graph form (Figs. 2 and 3).

From the figures presented the following facts emerge:

(*a*) The mean weights in both sexes at the time of operation were considerably below the "best ever" weights, but here other factors such as age may be responsible as well as the ulcer. This does not appear to apply in groups 4 and 5 results for gastric ulcer in women but the actual number of cases is so small that the figures are not significant.

(*b*) The mean weights in both sexes at the time of operation in all sub-groups were below the standard weight and very few individual cases were above standard weight.

(*c*) Patients who had achieved a good result from operation by the basic assessment appeared on the average to maintain or slightly increase their weight after operation, but the mean weights were still below the standard weights.

(*d*) Those who had an unsatisfactory result from operation failed on the average to maintain their pre-operative weight. The majority of weight losses in these patients appeared to be in the first year after operation.

(*e*) It may be of interest to note that the mean weights of groups 4 and 5 result cases in all sub-groups were slightly higher before operation than those of groups 1 and 2 result cases.

### Failures after Gastrectomy

Of the 826 cases followed up, 99 (12%) were not considered sufficiently satisfactory for one reason or another and have been classified as failures. This group of 99 patients consists of group 4 and group 5 results. In group 5 either further surgical or medical treatment had been required or the patient had expressed his or her dissatisfaction with the operation. In group 4, patients on the whole preferred their present state to the original ulcer but had in the investigators' opinion symptoms which prevented them leading a normal life. In the tables in which results of operation are compared with the series of factors much information is given regarding the group 4 and 5 cases. It is considered sufficiently interesting, however, to discuss these failures in a little more detail.

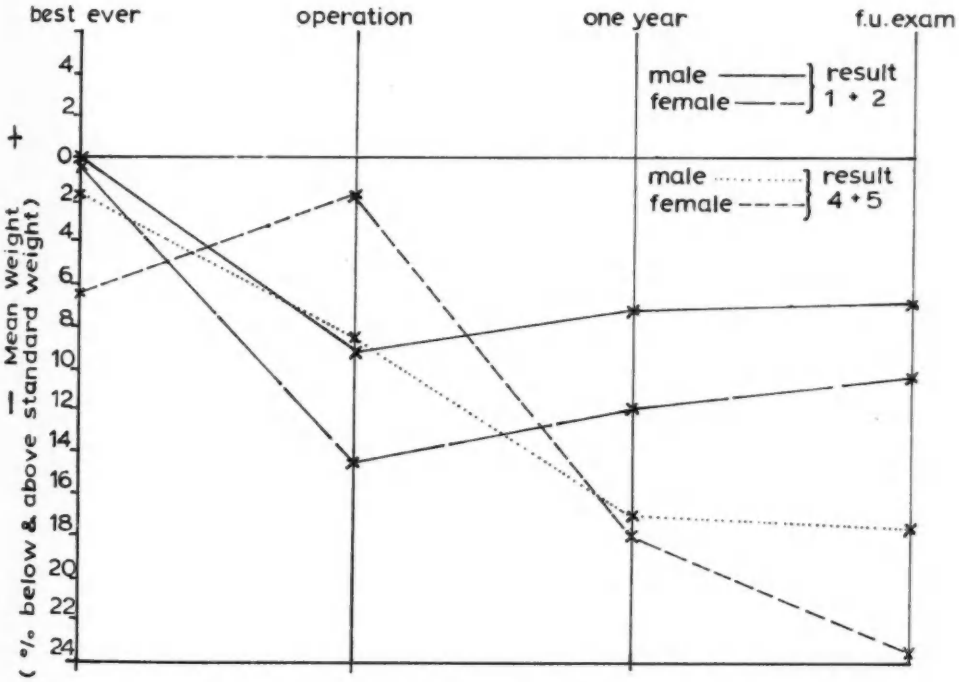


FIG. 2.—*Mean weights for both sexes for good and for unsatisfactory groups in duodenal ulcer cases.*

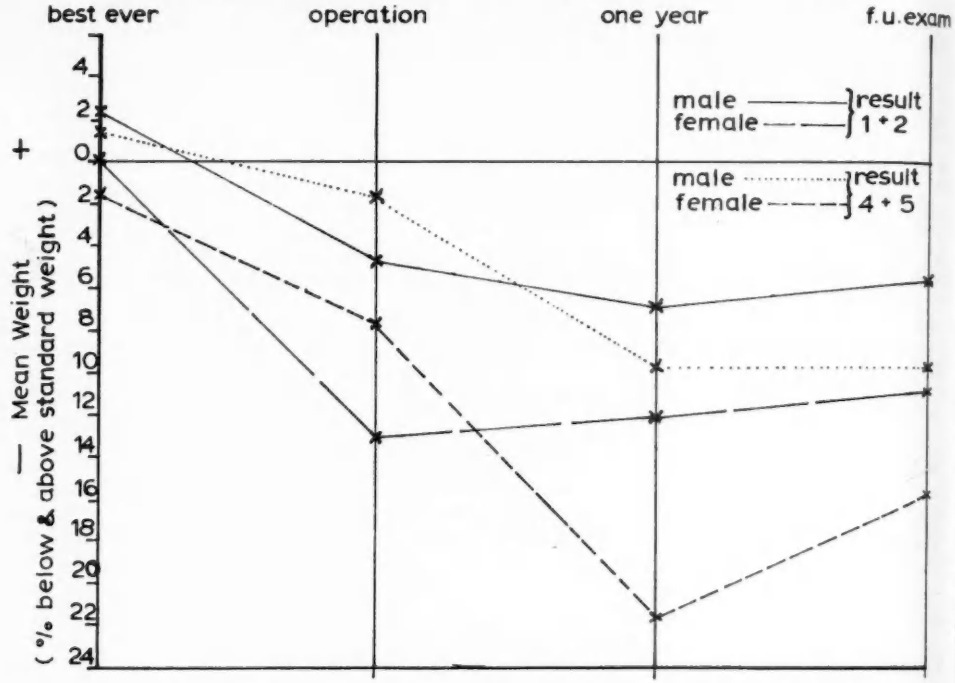


FIG. 3.—*Mean weights for both sexes for good and for unsatisfactory groups in gastric ulcer cases.*

GROUP 5 PATIENTS.—There were 57 patients in group 5, 6·9% of the total followed up. They are considered in the following sub-groups according to the chief symptoms or cause of failure (Table XVI).

*Bilious Vomiting: Afferent Loop Syndrome.*—Seventeen cases were classed as failures because of severe and persistent bilious vomiting, sometimes associated with other features of the afferent loop syndrome, and needed a further operation. In 12 cases the symptoms came on very soon after the original gastrectomy and only in one case was the onset later than 18 months. All occurred after a Polya type operation and in seven of the patients a Hofmeister modification of that operation had been done.

TABLE XVI

ANALYSIS OF GROUP 5 RESULTS

| Causes of Failure | Total No. | Original Operation | | | | | Original Ulcer | | | | Sex |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Retrocolic Polya | Antecolic Polya | Antecolic Polya Hofmeister | Retrocolic Polya Hofmeister | Billroth | Duodenal Ulcer | Gastric Ulcer | Duodenal and Gastric Ulcer | Stomal Ulcer after Gastro-enterostomy | Male |
| Bilious vomiting | 17 | — | 9 | 7 | 1 | — | 13 | 3 | 1 | — | 12 |
| Faintness, sweating, and post-prandial diarrhoea | 2 | — | 1 | 1 | — | — | 2 | — | — | — | 2 |
| Stomal ulcer | 15 | — | 8 | 4 | — | 3 | 13 | — | — | 2 | 14 |
| Steatorrhoea | 3 | — | 3 | — | — | — | 3 | — | — | — | 3 |
| Miscellaneous complications | 3 | — | 3 | — | — | — | 2 | 1 | — | — | 3 |
| Patient's verdict of "failure" | 17 | — | 11 | 5 | — | 1 | 8 | 8 | 1 | — | 16 |
| Total | 57 | — | 35 | 17 | 1 | 4 | 41 | 12 | 2 | 2 | 50 |

The second, or "corrective", operation was entero-enterostomy in eight cases, Polya to Billroth conversion in seven cases, and division of adhesions in one case only. Of the entero-enterostomies, seven patients have since improved sufficiently to be now equivalent to group 1 or 2 results and the other to group 4. Of the Polya to Billroth conversions, three are equivalent to group 1 or 2 results, one to group 3, and one to group 4, with two cases too early for assessment. In one case only were adhesions divided and that patient is only slightly improved. The remaining patient is of interest in that two years after operation he developed a rupture of the duodenum due to afferent loop distension. The duodenum was repaired as an emergency. He still has bilious vomiting and is awaiting further surgery for this.

*Faintness, Sweating after Meals, and Severe Diarrhoea.*—Two patients had this combination of symptoms after Polya gastrectomy and a Henley loop type of gastroplasty was subsequently carried out in both. Neither case subsequently showed any improvement.

*Steatorrhoea.*—Three cases were classified as failures because of the development of steatorrhoea after operation. In all three the steatorrhoea was severe enough to be incapacitating and had been proved by hospital investigation. All were men and steatorrhoea had followed antecolic Polya operations.

*Stomal Ulcer.*—Fifteen cases were considered to have developed stomal ulcer since operation. In 12 of these the diagnosis was based on the findings at a second operation, radiographs, or on evidence of post-gastrectomy intestinal haemorrhage. The other three patients had had ulcer-type symptoms very suggestive of recurrent ulcer.

Of the 15 patients, 13 had had gastrectomy for duodenal ulcer and the other two had had gastrectomy for a stomal ulcer following a previous gastroenterostomy for duodenal ulcer. Twelve of them occurred in patients who had had a Polya type operation and the other three had had Billroth gastrectomies. All except one were in men.

Re-operation was carried out in 10 cases, consisting of vagotomy in seven, conversion from Polya to Billroth in one, Henley loop gastroplasty in one, and extension of Polya gastrectomy in the other. Two cases after vagotomy are now symptom-free and one is improved. The case converted to Billroth improved slightly and is now equivalent to group 3, while the case after Henley loop gastroplasty was again a failure and needed excision of the jejunal loop. Other cases are too early to assess results.

*Miscellaneous.*—In three patients failure occurred but was perhaps not of the type usually classed as post-gastrectomy syndrome. In all three, however, it was considered that the original gastrectomy was indirectly responsible for their present incapacity. One had pulmonary tuberculosis before gastrectomy and this became much worse immediately after the operation. In the second the common bile duct was damaged surgically at the time of operation and the patient has had recurrent cholangitis since then. The third developed severe peritoneal infection after the operation which led to extensive adhesions and has needed four subsequent operations for intestinal obstruction with much disability. All three were men. These failures followed antecolic Polya operations. In two the original ulcer was duodenal, while the other had a gastric ulcer.

*Patient's Verdict of "Failure".*—Seventeen patients at interview stated that their present condition was worse than that before gastrectomy and that they were sorry they had had the operation performed. Their symptoms and complaints were too varied and multiple to classify into any particular group. Faintness after meals, inability to take large meals, lassitude, occasional bilious vomiting, abdominal discomfort after meals, loss of appetite, and nausea were the most frequent symptoms. One patient had had a subsequent Henley loop gastroplasty performed without improvement. Another had needed an operation for volvulus of the gastric stump. Four patients had needed subsequent psychiatric treatment for depressive psychoses. In none was the clinical picture of the symptoms, nor, in some, the results of investigations sufficient to warrant further surgery. Furthermore, in this group on the whole, the patients voiced the opinion that they would not consider further operation even if it were raised. It was our impression that possibly the fault in these patients lay in original misjudgments in selecting cases for gastrectomy.

In this group 16 of the 17 failures were in men; eight followed operations for gastric ulcer, one for gastric and duodenal ulcer, and eight for duodenal ulcer. The proportion of men and of gastric ulcer types is higher in this group than in the total series. Sixteen of these patients had had antecolic Polya operations, five of them of the Hofmeister modification. One patient had had a Billroth gastrectomy.

GROUP 4 PATIENTS.—In group 4 there were 42 patients, representing 5·1% of the total followed up. None, of course, had required further surgery as far as the gastrectomy was concerned, none had recurrent ulcers, and none of the patients had expressed complete dissatisfaction with the opera-

TABLE XVII
ANALYSIS OF GROUP 4 RESULTS

| Causes of Failure | Total No. | Original Operation | | | | | Original Ulcer | | | | Sex | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Retro-colic Polya | Ante-colic Polya | Ante-colic Polya Hofmeister | Retro-colic Polya Hofmeister | Billroth | Duodenal Ulcer | Gastric Ulcer | Duodenal and Gastric Ulcers | Stomal Ulcer after Gastro-entero-stomy | Male | Female |
| Bilious vomiting | 21 | 2 | 10 | 6 | 2 | 1 | 8 | 12 | 1 | — | 17 | 4 |
| General weakness | 1 | — | 1 | — | — | — | — | 1 | — | — | — | 1 |
| Faintness and sweating, etc., after meals | 10 | 1 | 6 | 1 | 2 | — | 7 | 3 | — | — | 7 | 3 |
| Discomfort after average-sized meal | 4 | — | 3 | 1 | — | — | 2 | 2 | — | — | 4 | — |
| Steatorrhoea or post-prandial diarrhoea | 6 | 1 | 2 | 3 | — | — | 3 | — | 2 | 1 | 4 | 2 |

tion. These factors would have made them group 5 results. In our original analysis we had classified the patients according to their chief post-gastrectomy symptoms rather than to particular groups of symptom complexes. We did this because we found so many cases in which the patient's particular collection of symptoms did not always fit into any one set post-gastrectomy syndrome. In Table XVII, analysing group 4 results, we have classed the patients according to the main symptoms of which they complained. Hence 21 of the 42 patients in this group complained chiefly of bilious vomiting although some of them also had faintness or abdominal discomfort after meals which did not particularly worry them. Similarly 10 complained chiefly of faintness after meals, four of discomfort after an average-sized meal, and six of steatorrhoea, but some of these also had mild, infrequent bilious vomiting. One of the patients in this group with steatorrhoea had, in fact, got the steatorrhoea before the gastrectomy, since it had followed a gastro-enterostomy for duodenal ulcer.

## Summary

A detailed survey has been made of 955 patients in whom partial gastrectomy was performed for peptic ulcer. The operative mortality rate was 3·87% (37 patients). Of 876 cases available for investigation, 826 (94·3%) were traced and interviewed. After the operation 540 patients (65·4% of those followed up) were able to lead a normal life and had no symptoms of any significance, while a further 187 (22·6%) had mild symptoms which needed some dietary care or medical treatment, but which did not prevent them leading a normal life. The remaining 99 were unsatisfactory results and of these 57 (6·9%) patients were as bad as, or worse than, before operation.

The result of the operation did not appear to be influenced by the following factors: (1) Length of follow up, (2) age, (3) site of ulcer, (4) duration of symptoms before operation, or (5) the type of pre-operative symptoms. Men appeared to give better results than women to a degree just significant.

The Billroth operation gave better results in gastric ulcer, but for duodenal ulcer that operation gave equally good results to the Polya type. The variations of the Polya operation did not materially alter the results. The extent of gastric resection in both operations did not appear significant, except in men with duodenal ulcer (the largest group) where more limited resections (less than two-thirds) were significantly better.

In the satisfactory results earning capacity was increased and time lost from work reduced. The mean body weight before operation was considerably below the standard weight, and although in the satisfactory patients it showed slight improvement after operation, it still did not approach the standard weight.

The causes of failure in the unsatisfactory cases, some of which improved after further surgery, are analysed.

We should like to express our gratitude to the surgeons and physicians of the Queen Elizabeth Hospital, Birmingham, for allowing us to investigate these cases, and also particularly to Professor Stammers for his encouragement, help, and advice throughout the investigation.

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# A REPORT OF TWO CASES OF WHIPPLE'S DISEASE DIAGNOSED BY PERORAL SMALL INTESTINAL BIOPSY

BY

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Two patients with Whipple's disease are described in whom the diagnosis was established by peroral small intestinal biopsy. Scurvy occurred in one patient.

Whipple's disease was first described in 1907. It is a rare disease, affecting predominantly men in middle life. Its clinical manifestations are those of a malabsorption syndrome. Certain other features, such as generalized lymphadenopathy and polyserositis or a history of preceding fleeting polyarthritis, lead to suspicion of Whipple's disease.

Fleeting arthritis may precede the diarrhoea and steatorrhoea by many years. Diagnosis rests essentially on histological grounds, the typical features being infiltration of macrophages into the wall of the small intestine and into mesenteric and sometimes peripheral lymph nodes. These macrophages contain a material which gives a purple-pink reaction with periodic-acid-Schiff stains, thus identifying it as mucopolysaccharide. In addition large cystic spaces are seen in these tissues, which may be dilated lymphatics, containing sudanophilic material.

The diagnosis of Whipple's disease usually presents difficulties. Until 1947 diagnosis was generally made at necropsy only. With wider recognition of the symptoms, diagnostic laparotomy became a recognized procedure. In 1955, Puite and Tesluk described for the first time three patients in whom the diagnosis of Whipple's disease was established by peripheral gland biopsy. But others (Upton, 1952) found the histology of similar glands unhelpful, and were forced to proceed to laparotomy.

We report two cases of Whipple's disease in order to call attention to the possibility of making the diagnosis by peroral small intestinal biopsy (Shiner, 1956) and also because of certain unusual features noted in one of our cases.

## Case Reports

Case 1.—A man, aged 35, had had no significant previous illnesses except occasional attacks of diarrhoea in the tropics while in the Navy. His present illness began in 1946 with fleeting arthritis affecting the shoulders and knees. This subsided in a few months. In 1950 arthritis, affecting mainly the joints of the wrists and fingers, recurred. It was not until 1955 that he began to complain of colicky abdominal pain, sometimes accompanied by vomiting. In March, 1956, he developed a purpuric rash on the legs and also bleeding of the gums. The diagnosis of scurvy was then made at another hospital and the skin and gum manifestations cleared up within a few days of receiving two doses each of 4 g. of ascorbic acid orally. He was maintained on two capsules of "vitaminorum", N.F., daily and remained fairly well for the next five months. Thereafter he deteriorated, complaining of weakness, cough, diarrhoea, and increasing pigmentation, and he was finally admitted under Dr. Litchfield to St. Mary's Hospital in August, 1957.

On examination he was a thin, ill-looking man. There was brown pigmentation of the face and palate. The axillary and inguinal glands were moderately enlarged. The abdomen was somewhat distended and doughy in consistency. The liver and spleen were not felt. The joints appeared normal. Blood pressure was 90/60 mm. Hg. Biopsy of one inguinal gland showed a considerable amount of periodic-acid-Schiff-positive staining material but a similar lymph node taken from a control subject contained the same material, though to a lesser extent. Results of the investigations are summarized in Table I.

*Further Progress.*—On admission the vitamin supplements were discontinued and he was given an ordinary ward diet. Ten days later a perifollicular purpuric rash appeared on the legs, accompanied by bleeding from the gums. A diagnosis of scurvy was made. The clinical manifestations of scurvy subsided within a few days of treatment with 700 mg. ascorbic acid a day by mouth. Table II shows the results of the ascorbic acid saturation test. The excretion of over 50 mg. ascorbic acid/10 stone body weight has been considered by Harris (1943), using a slightly different form of the test, to mark the approach

TABLE I
RESULTS OF INVESTIGATIONS

| Investigation | Case 1 | Case 2 |
|---|---|---|
| Haemoglobin | 80% (11·7 g./100 ml.) Normal film | 32% (4·6 g./100 ml.) Film showed evidence of gross iron deficiency. |
| White cell count | 6,000 (normal differential count) | 5,800 (normal differential count) |
| Prothrombin time (one-stage) | 19 sec. (control 14) | 13 sec. (control 11) |
| E.S.R. (Westergren, one hour) | 26 mm. | 35-130 mm. |
| Serum electrolytes: | | |
| Sodium | 136 mEq./l. | 132 mEq./l. |
| Chloride | 100 mEq./l. | 98 mEq./l. |
| Potassium | 4·4 mEq./l. | 3·1 mEq./l. |
| Bicarbonate | 28·2 mEq./l. | 20 mEq./l. |
| Serum proteins | | |
| Total | 6·6 g./100 ml. | 4·8 g./100 ml. |
| Albumin | 3·8 g./100 ml. | 2·2 g./100 ml. |
| Globulin | 2·8 g./100 ml. (normal *globulin* fraction) | 2·6 g./100 ml. (high *globulin* fraction) |
| Serum calcium | 9·2 mg./100 ml. | 7·8 mg./100 ml. |
| Serum inorganic phosphate | 3·7 mg./100 ml. | 3·0 mg./100 ml. |
| Serum alkaline phosphatase | 8·7 K.-A. units/100 ml. | 6·1 K.-A. units/100 ml. |
| Serum cholesterol | 89 mg./100 ml. | Not estimated |
| Serum $B_{12}$ concentration | Not estimated | 305 μμg./ml. |
| Folic acid absorption test | Not done | Normal |
| Rose-Waaler test | Not done | Normal, *i.e.*, negative, < 1 : 8 |
| Total faecal fats (3-day collection, patient on normal diet) | 23·6 g./day | 18 g./day |
| Occult blood in stools | Consistently positive | Intermittently positive |
| Glucose tolerance test (standard, oral) (half-hourly) | 60-75-70-70-62 | 112-117-153-163-144 |
| Pancreatic enzymes | Trypsin found in stools | Normal (by duodenal aspiration) |
| Barium meal and follow-through | Deficiency pattern | Mild deficiency pattern |
| Peripheral lymph node biopsy | Inconclusive | No enlarged glands felt: biopsy not performed |

of saturation. In our patient this did not occur until he was given 2 g. ascorbic acid daily by mouth.

TABLE II

| Date | Urinary Ascorbic Acid Level (mg.) (10 a.m.-3 p.m.) | Dose of Ascorbic Acid Given at 8 a.m. |
|---|---|---|
| Oct. 15, 1957<br>Oct. 28, 1957 | 22·0<br>5·5 | 0·7 g./day (oral) continued in same dose until: |
| Oct. 29, 1957 | 18·5 | Single dose of 0·7 g. intravenously |
| Nov. 1, 1957<br>Nov. 4, 1957 | 52·0 | 2·0 g./day (oral) continued in same dose |

On additional treatment with a low-fat diet and mist. bismuth *et opii*, the diarrhoea diminished and he was able to return to work for the next six months. His improvement was not maintained and a further exacerbation of diarrhoea, accompanied by weight loss and weakness, necessitated his second admission to hospital in July, 1958. Treatment with A.C.T.H., 120 units, daily, was then begun and later changed to oral prednisone, 80 mg. daily, and finally to intravenous hydrocortisone. Despite this, his condition continued to deteriorate and he died two months after admission. Post-mortem examination revealed gross atrophy of the small intestinal mucosa together with widespread enlargement of the lymph glands, particularly marked in the mesenteric glands. In addition there were vegetations on two of the cusps of the aortic valve.

CASE 2.—A man aged 47, mentally defective owing to severe birth trauma, had had no serious illnesses until 1954, when he began to lose weight and complained of vague general ill health. In 1955, there was transient swelling of the legs and hands with pitting oedema, and he complained of pain in the legs, back, neck, and shoulders. Between 1955 and 1957 he had frequent attacks of winter cough. Early in 1957 he began to have diarrhoea, passing two to four pale, bulky, offensive-smelling stools daily. Thereafter his rapid weight loss and increasing breathlessness led to investigation at his local hospital where a diagnosis of idiopathic steatorrhoea was made. Despite a low-fat diet and supplements of iron and folic acid by mouth he deteriorated still further and was admitted to the Middlesex Hospital under Professor Kekwick in September, 1957.

On examination he was desperately ill. He was pale and dyspnoeic, with gross oedema of the legs, thighs, and abdominal wall, tense ascites, bilateral purulent conjunctivitis, clubbing of the finger and toe nails, and a raised jugular venous pressure. The muscles were very wasted and his skin was dry, inelastic, and slightly pigmented. The peripheral lymph glands were not palpable. Widespread rales and rhonci were heard in all areas of the chest. Investigations are summarized in Table I.

Energetic treatment with penicillin, digitalis, transfusion of packed cells, parenteral iron, and vitamins resulted in rapid improvement after 10 days.

*Further Progress.*—His illness followed a fluctuating course with episodes of fever, diarrhoea, and a painful effusion into the right knee joint two months after admission. He improved for a considerable time after this and remained well for nine months, although he still had diarrhoea and a hypochromic anaemia resistant to parenteral iron therapy. Because of general deterioration and increasing anaemia he was readmitted to hospital in November, 1958.

Symptomatic treatment of diarrhoea did not help, and he was started on prednisone, 10 mg. t.d.s. He

improved a little and the diarrhoea diminished. Ten days after starting prednisone he suddenly collapsed with signs of acute peripheral circulatory failure and died.

Post-mortem examination showed maldevelopment of the left cerebral hemisphere and vegetations on a bicuspid aortic valve. The whole length of small intestine was grossly distended with thin black fluid and its wall showed extreme congestion and oedema. There was no obstruction of the mesenteric arteries and histological examination did not suggest infarction. Culture of the small bowel contents yielded only *B. proteus* and coliform bacilli. Histological examination of the small intestinal wall and mesenteric lymph glands confirmed the diagnosis of Whipple's disease. The cause of death seems obscure but could possibly have resulted from rapid transit of fluid from the circulation to the gut lumen.

### Histology

Case 1.—Three mucosal specimens were obtained by peroral intestinal intubation from the upper part of the jejunum. These included full-thickness mucosa (Fig. 1a). The villi appeared markedly distended, shortened, and clubbed, due to numerous macrophages in the villous stroma (Fig. 1b). Similarly, the interglandular stroma of the lamina propria was seen to contain macrophages but to a much lesser degree. With the periodic-acid-Schiff stain these macrophages stained a purple pink.

Goblet cells were seen in excess in between villous and glandular cells and there was also some increase in inflammatory cells, mainly in the form of polymorphonuclears, both in the mucosa and submucosa.

Case 2.—Six full-thickness mucosal specimens were obtained from the first part of the jejunum. All showed periodic-acid-Schiff-positive staining macrophages, distributed mainly in the interglandular stroma of the lamina propria (Figs. 2a and b). In contrast to Case 1, the villi, though irregular in shape, were of normal height and width and the upper third of the villi was almost entirely free from macrophage infiltration, whereas the glandular layer was much increased in thickness. No increase in goblet or inflammatory cells was observed.

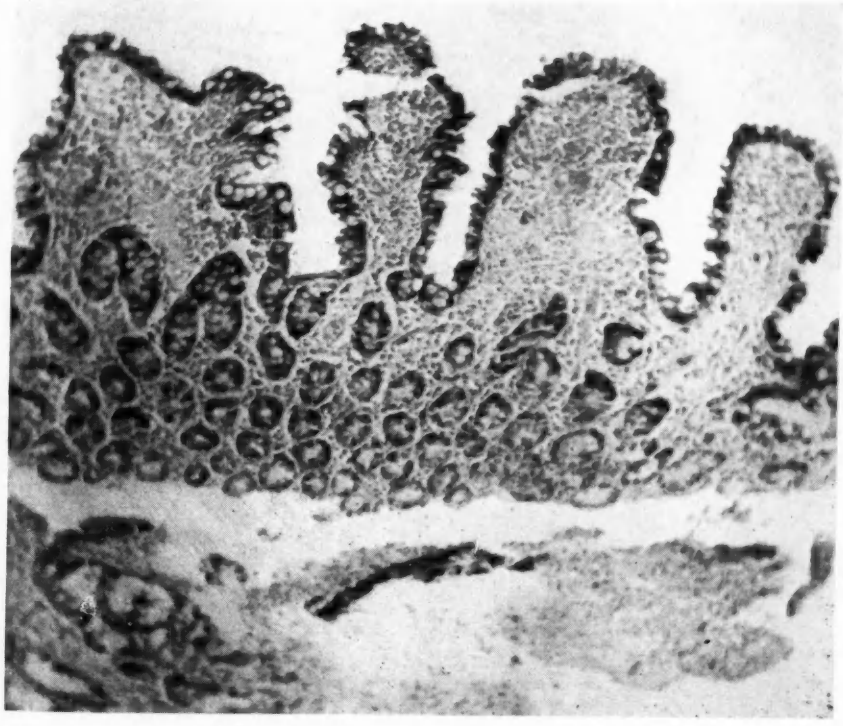

Fig. 1a.—*Low-power view of jejunal mucosa from Case 1, showing shortening and distension of villi due to cellular infiltration and an increase in goblet cells. Haematoxylin and eosin* × *100.*

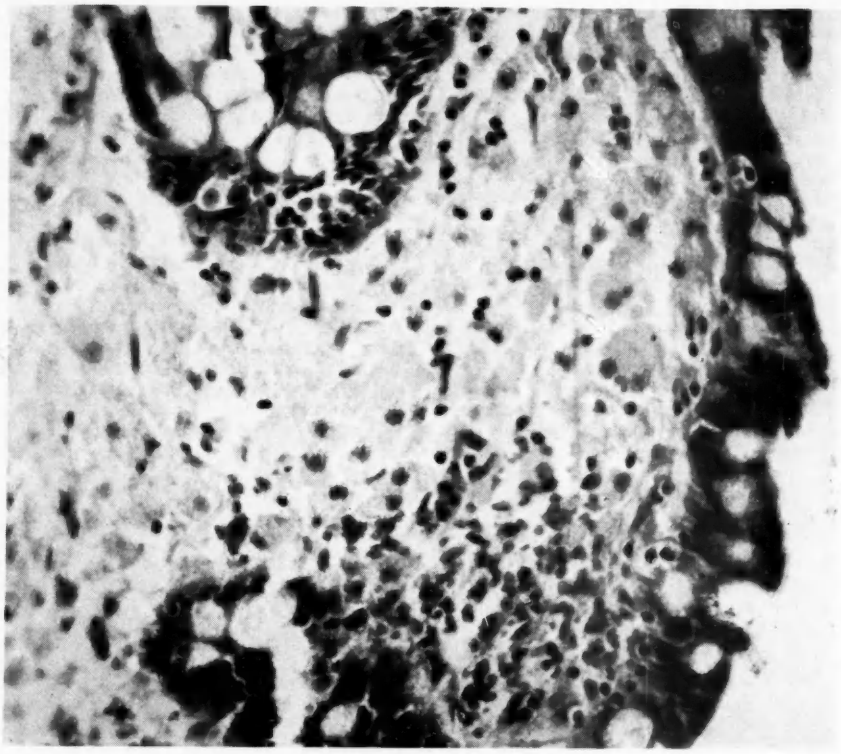

FIG. 1b.—*High-power view of a distended villus from Fig. 1a, arrows pointing to typical macrophage cells. Haematoxylin and eosin* × *400.*

## DISCUSSION

Whipple's disease is almost invariably fatal, the duration of the illness lasting from five to 10 years or longer from the onset of first symptoms. Scurvy is a well-recognized complication of the malabsorption syndrome but is uncommon. Still (1918) reported it in four cases of coeliac disease but it has not, to our knowledge, previously been described in Whipple's disease.

The slow response of the urinary ascorbic acid excretion as compared with the rapid clinical improvement as soon as treatment with ascorbic acid is begun, is known to occur in scurvy (Schultzer, 1936). In addition, Boscott and Cooke (1954) drew attention to the fact that saturation with ascorbic acid may be delayed in steatorrhoea and that this may occur even when the ascorbic acid is given parenterally. The daily requirements of ascorbic acid are somewhat controversial. Minimal daily requirements have been quoted as 15 mg. (Kellie and Zilva, 1939) to 75 mg. (Scheunert, 1949). After the first attack of scurvy, the normal diet of Case 1 was supplemented with 30 mg. ascorbic acid and two oranges daily (providing about 100 mg. ascorbic acid). Only 10 days after discontinuing these supplements he developed frank scurvy. A normal volunteer maintained on a vitamin-C-deficient diet did not develop scurvy until he had been on this diet for 161 days (Crandon, Lund, and Dill, 1940). In a similar experiment performed upon himself in the eighteenth century, William Stark developed scurvy only after two months (Drummond and Wilbraham, 1935). The rapidity with which our patient developed scurvy suggests that his previous intake of ascorbic acid represented what was for him the critical minimum requirement.

We have no information in Case 2 about his absorption of ascorbic acid, since large doses were

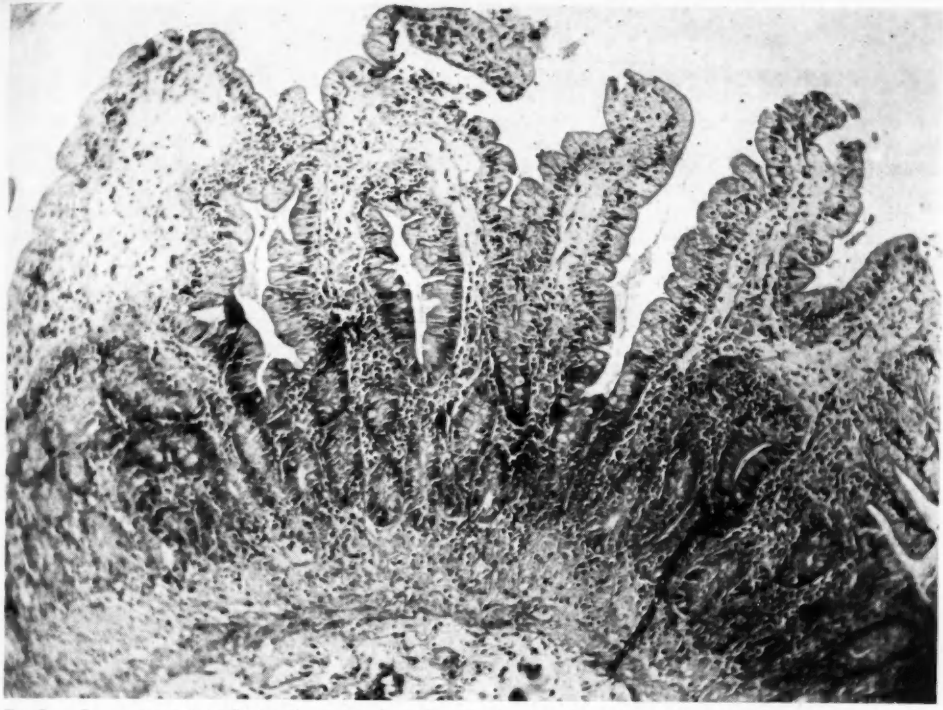

FIG. 2a.—*Low-power view of jejunal mucosa from Case 2, showing long villi free from cellular infiltration in their upper parts. Cells are densely packed in the intervillous stroma of the lower part of the villi and whole thickness of mucosa. Haematoxylin and eosin* × *100.*

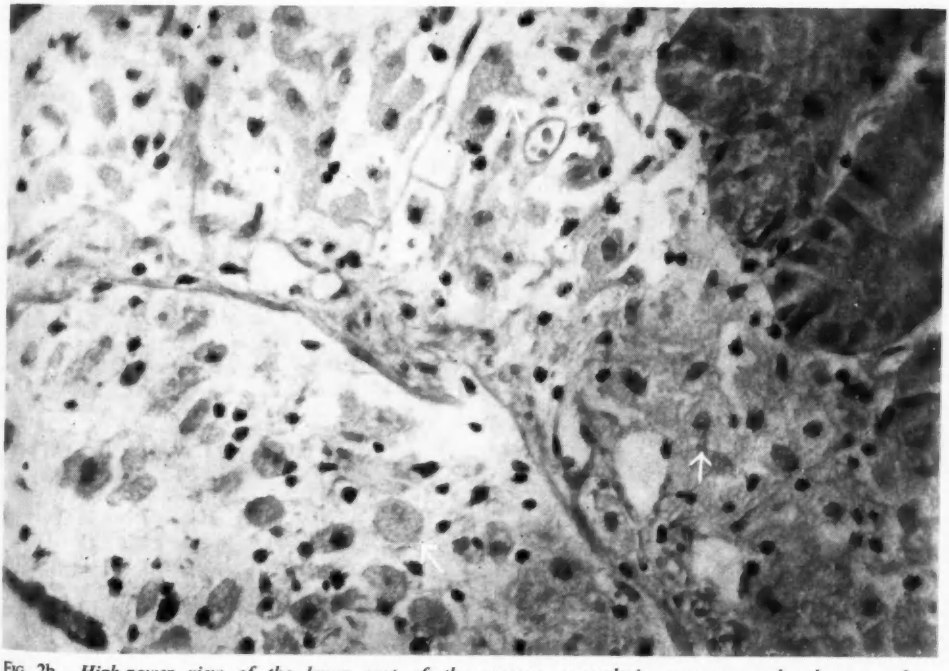

FIG. 2b.—*High-power view of the lower part of the mucosa, muscularis mucosae, and submucosa from Fig. 2a, arrows pointing to macrophages above and below muscularis mucosae. Haematoxylin and eosin* × *400.*

given as part of his initial emergency treatment. Although our second case showed evidence of malabsorption of fat, of protein, and probably of vitamin D, it is interesting to note that his absorption of folic acid was normal. This is in contrast to most cases of idiopathic steatorrhoea (Chanarin, Anderson, and Mollin, 1958). The serum $B_{12}$ concentration was also normal.

Diagnosis of Whipple's disease by peroral intestinal biopsy causes little discomfort to the patient and avoids laparotomy. It should be carried out at an early stage in all cases suspected of Whipple's disease. The characteristic histological picture of Whipple's disease has been looked for in all of the 200 or more intestinal biopsies performed by the peroral method but has only been seen in the two cases described in this paper. These 200 biopsies included 75 cases of steatorrhoea from various causes.

Because of the poor prognosis in Whipple's disease, much discussion has evolved around the question of treatment with steroids or A.C.T.H. It has been stated by some authors (Wang, Janowitz, and Adlersberg, 1956; Schaffner and Scherbel, 1955) that the disease may be favourably influenced by steroids in its early stages. They reported on patients who showed improvement on corticoids over a follow-up period of 20 and 10 months respectively. However, the course of the disease is a long one with periods of exacerbations and remissions; and therefore any beneficial effect attributed to steroids must be interpreted with caution.

Repeated biopsies at various stages after treatment in Whipple's disease might give us objective evidence of improvement or otherwise. Finally, histochemical stains on the mucosal specimens may in the future enable the identification of the mucopolysaccharide material contained in the macrophages.

We are most grateful to Dr. J. W. Litchfield and to Professor A. Kekwick for kindly allowing us to study and report these cases under their care, and for their encouragement. We also wish to acknowledge the help and advice given to us by Dr. T. M. Chalmers, Dr. R. H. Heptinstall, Professor I. Doniach, Dr. R. A. B. Drury, Dr. J. F. Arthur, and Dr. R. Cotton. Dr. D. L. Mollin kindly performed the $B_{12}$ estimations and Dr. I. Chanarin the folic acid absorption test; we are grateful for their permission to report the results. One of us (M.S.) gratefully acknowledges the assistance of the Medical Research Council from which a grant was received.

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*Gut*, 1960, **1**, 169.

# HEPATIC NECROSIS DUE TO MARSILID

BY

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In the patient reported here severe jaundice and death resulted from treatment with iproniazide ("marsilid") given for only three days.

Iproniazide ("marsilid") is now well recognized as a cause of jaundice due to liver cell damage. The following case report is exceptional in that death followed the administration of a very small dose of iproniazide given over 72 hours.

## Case History

A 64-year-old woman was admitted to Wood Green Hospital on August 7, 1959. For the previous 18 months she had suffered from severe angina pectoris, and on July 10, iproniazide, 50 mg. T.D.S., had been prescribed. Two days later, on account of anorexia and slight nausea, the dose was reduced to 12·5 mg. T.D.S. for one further day and then stopped. Two weeks later slight jaundice developed and her urine became dark. There was no pruritus and no previous history of jaundice or of contact. She was observed at home for two weeks but was then admitted to hospital in view of deepening jaundice. She had lost a stone in weight over the month just before admission.

On examination she was deeply jaundiced but mentally alert. Neither liver nor spleen were palpable and the area of liver dullness was reduced. She was slightly tender in both hypochondria. Her blood pressure was 160/90 mm. Hg. No other physical signs were obtained.

Investigations.—The serum bilirubin test was 40 mg.%, the Van den Bergh reaction positive, serum alkaline phosphatase 27 King-Armstrong units. Flocculation tests were negative. S.G.O.T. was 44 units. Blood urea was 84 mg.%. Hb was 12·8 g. (87%) and W.B.C.s numbered 6,000 per c.mm. The differential count was normal. Some target cells were present on the blood film. Radiographs of the chest and abdomen were normal.

Treatment.—Glucose drinks, vitamin supplements, and triamcinolone, 5 mg. T.D.S., were given.

On August 15 slight mental confusion was noticed for the first time. The bilirubin level had now fallen to 30 mg.%. On August 28, in view of increasing mental confusion, she was transferred to Hammersmith Hospital. On admission she was semi-comatose. Deep jaundice was present and slight foetor hepaticus was noted. There was no flapping tremor or muscular hypertonia. There were no skin stigmata of chronic liver disease. Neither liver nor spleen was palpable and there was resonance to percussion over the entire liver area. There was no ascites but slight sacral oedema. Blood pressure was 160/90 mm. Hg. A few basal rales were present. There were no further physical signs.

Investigations.—An analysis of the urine showed bile but not urobilinogen. Microscopically the urine was normal.

Prothrombin time was 19 sec. (26-35%), Hb 15·8 g. (107%), P.C.V. 56%, M.C.H.C. 28%, platelets 150,000 per c. mm., W.B.C.s 22,000 (neutrophils 93%, lymphocytes 4%, monocytes 3%, reticulocytes 3%).

Liver function tests showed that bilirubin was 30mg.%, cholesterol 149 mg.%, alkaline phosphatase 31 King-Armstrong units, thymol turbidity 1 unit, zinc sulphate 1 unit. Total protein was 5·8 g. (albumin 3·0 g., globulin 2·8 g.). Electrophoresis was normal. S.G.O.T. was 77 units and S.G.P.T. 55 units.

The bicarbonate level was 24 m.Eq./l., sodium 111 m.Eq./l., potassium 3·5 m.Eq./l., chlorides 78 m.Eq./l., and urea 130 mg./100 ml.

Treatment.—Neomycin, potassium chloride, and high doses of steroids were given. Glucose 20% was given intravenously and vitamin supplements intramuscularly. Regular bowel motions were ensured by oral magnesium sulphate and bowel washouts as required.

On the morning after admission her blood pressure fell over a few hours to 80/60 mm. Hg. As the haemoconcentration, low serum sodium, and raised blood urea, in addition to the fall in blood pressure, pointed to a low sodium state, 500 ml. of 5% sodium chloride was given intravenously. This caused no change in the level of blood pressure, which was later temporarily raised by a noradrenaline infusion. There was no improvement in her general condition, however, and she died 36 hours after admission.

A liver biopsy taken a few minutes after death showed ballooning and hyaline change of the liver cells, quite large numbers of which were necrotic. Considerable biliary retention was present, particularly in the canaliculi. There was slight infiltration of the portal tracts (Prof. C. V. Harrison).

Post-mortem examination confirmed that the liver

was very small; in fact it weighed only 700 g. (normal 1,450 g.). Microscopy of liver sections obtained at necropsy showed that the liver cell destruction was patchy and periportal; it was not centrilobular.

## Discussion

In this case, as in most of the recorded cases, it is not possible to distinguish the clinical picture from that of acute hepatic necrosis due to infective hepatitis. The absence of centrilobular necrosis in the liver sections from this patient shows, however, that this was not hepatic necrosis due to infective hepatitis. Another important point is that in this patient 337·5 mg. of iproniazide caused death. No case history could be found in the literature in which so small a dose of iproniazide caused a fatal result. Floody, Dixon, and Mattia (1958) state that the amount of iproniazide given to 13 fatal cases ranged from 300 to 8,000 mg. They give no details and most of the information seems to have been obtained from questionnaires. Benaim and Dixon (1958) quote Marks as saying that jaundice may occur with as little as 25 mg. and that the duration of therapy is not important.

It has been said (Pare and Sandler, 1959) that in patients on iproniazide serial transaminase values may rob the drug of one of its great hazards to life. From our experience with this case it would seem that it may be too late to stop the drug when the transaminase values become raised.

We wish to thank Professor Sheila Sherlock for permission to publish this case.

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*Gut*, 1960, **1**, 171.

# SMOKING AND THE ALIMENTARY TRACT: A REVIEW

BY

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Because of inherent and inseparable variables, studies of the effect of smoking on gastric secretion and motility have proved inconclusive. The only firm conclusions to be drawn from the work reviewed are that the prognosis of both gastric and duodenal ulcers is made worse by regular smoking and that the healing and response of gastric ulcers to medical treatment is impaired. The mechanisms through which these effects are produced are unknown. It is not even certain that nicotine is the chief noxious agent in tobacco. Careful statistical and epidemiological studies have yielded such facts as exist and this approach seems the most promising one for future studies.

## Pharmacology of Tobacco

Nicotine renders ganglion cells at first more sensitive and then more resistant to acetylcholine; there is therefore a transient stimulation followed by a more persistent depression of autonomic ganglia. The response to post-ganglionic stimulation is unimpaired. The effect of nicotine at any moment thus depends upon a summation of opposing effects. Salivary flow, for instance, may be stimulated then depressed. The subcutaneous injection of nicotine has been shown to cause nausea and vomiting, increased motor activity of the bowel, and perhaps diarrhoea with subsequent depression of intestinal tone and motility. This effect on the bowel can be blocked by atropine (Goodman and Gilman, 1955). It will be seen that the effects of smoking are less clear-cut than those of nicotine.

Nicotine is found in tobacco leaf as the salt of organic acids. Heat liberates the free base, which passes partly into the smoke where some is burned, but variable amounts enter the respiratory tract and are absorbed. The mean concentration of nicotine in cigarette tobacco is about 1·5% and the smoke from one cigarette may produce 6-8 mg. of nicotine. Of this, 3-4 mg. may be absorbed but the amount depends upon the moisture of the tobacco, the speed of smoking, the amount of inhalation, and the presence of a filter or cigarette holder. It is dependent also upon whether pipe, cigar, or cigarette is smoked (Goodman and Gilman, 1955; Batterman, 1955).

It is not clear how far the effects of smoking are due to nicotine, for tobacco contains other substances which may be important: nornicotine, pyridine and other nitrogenous bases, volatile acids, tars, and phenols. These probably contribute to mucosal irritation but it is uncertain whether their concentration is high enough for systemic effects, although pyridine bases, for example, have been shown to cause nausea, vomiting, diarrhoea, and peripheral circulatory collapse (Dixon, 1927).

## Effects of Smoking on the Stomach and Duodenum

When these factors and the variety of impulses which influence gastric function are considered, it is hardly surprising that studies of the effects of smoking on gastric motility and secretion in health and disease have produced widely divergent findings. Wolf and Wolff (1943) found in their subject, Tom, that when he was out of sorts and smoking was unpleasant he became nauseated, stomach contractions ceased, the mucosa blanched, and secretions diminished. No such changes were observed when he was in good humour and found smoking pleasant. It has been pointed out, too, by Haag and Larson (1944) that the effect of smoking in a basal subject may bear little relation to its effect in a subject who is up and about. Such observations give some idea of the many variable factors involved.

Gastric Motility.—Inconstant changes in gastric motility are recorded after smoking. It has been observed in man and dog that whereas 1 mg. of nicotine subcutaneously has no effect, a few puffs of cigarette smoke may largely inhibit hunger contractions for an hour (Carlson, 1916; Schnedorf

*This review was written while the author was the Royal Australasian College of Physicians' travelling scholar in medicine for 1959.

and Ivy, 1939). Perhaps this is the basis for the anorexia attributed to smoking but such inhibition has not been a constant finding in man. Batterman (1955), using intragastric balloons, showed three types of response in normal subjects and ulcer patients after smoking one cigarette. In one-third there was no effect, another third showed complete inhibition of motor activity for a time, and in the rest a period of hypermotility was followed by normal or subnormal activity. Batterman further observed that two cigarettes might sometimes cause an increase in motility and epigastric pain where one had no effect. Other workers have found that smoking has no significant effect on gastric emptying or motility (Schnedorf and Ivy, 1939; Dickson and Wilson, 1924; Steigmann, Dolehide, and Kaminski, 1954; Cooper, Harrower, Stein, and Moore, 1958).

Gastric Secretion.—Smoking appears to produce more variable effects still on gastric secretion. Although some workers have found an increase in gastric secretion after smoking, most have observed no change. Some of the discrepancies can be explained by lack of a satisfactory and reproducible test of secretory function.

Schnedorf and Ivy (1939) investigated the effect of smoking on gastric secretion in non-smokers, smokers, and patients with duodenal ulcer. They found in all groups that just over one half showed an appreciable decrease in volume and acidity, a little over 40% showed no change, and in a few there was an increase in acidity in fasting specimens. In dogs with tracheotomies and Pavlov pouches they observed that two cigarettes caused slight depression in volume and acidity. In neither man nor dog was an effect on the secretory response to food observed. In a careful study in 147 male patients with duodenal ulcer, Cooper and Knight (1956) assessed the effect of smoking on volume, free acid, *p*H, and concentration of pepsin. No significant difference was observed between the group which smoked and that which refrained. Others have made similar observations (Schliephake and Simmet, 1944; Hodges and Gilmour, 1950).

Other workers have found an increased acid output after smoking (Moll and Flint, 1928; Ehrenfeld and Sturtevant, 1941; Steigmann *et al.*, 1954). Steigmann *et al.* (1954) observed the acid output after smoking in 44 normal subjects and 54 ulcer patients. They found that whereas in half the normal subjects the output of acid was increased after smoking, it was increased in over 90% of the ulcer patients. They concluded that ulcer patients show a greater acid response to smoking than normals. Piper and Raine (1959) attempted to eliminate one of the many variables by employing the augmented histamine test (Kay, 1953) as a measure of gastric secretion. They investigated 12 smokers, namely, three healthy students, three patients with peptic ulcer, and six patients with diseases not known to affect gastric function. All were fasting, none had smoked for 10 hours before the test, and in all the test was repeated. Basal secretion was estimated for one hour, each subject smoked four to six cigarettes during the second hour, and the augmented histamine test was performed in the third hour. On another occasion each subject was studied for two basal hours only so that each acted as his own control. Volume, total acid, and chloride content of gastric juice were found to be increased by smoking. The advantage of this over other studies lies in the fact that a reproducible test of gastric function was employed; other variables remained.

## Effect of Smoking on Dyspepsia and Peptic Ulcer

Many observers have commented that smoking aggravates dyspeptic symptoms (Gray, 1929a, b; Hurst and Stewart, 1929; Bockus, 1944; Schindler, 1947). Such observations have largely been uncontrolled and are dependent on subjective evidence. Jamieson, Illingworth, and Scott (1946) performed a more careful study. On questioning 473 ulcer patients they found that heavy cigarette smoking was associated with severe symptoms and pipe smoking with mild symptoms; a change in smoking habits did not influence the severity of symptoms. It was felt that this association was indirect and dependent on age, since severe symptoms and cigarette smoking tend to occur in the young while pipe smokers are older patients with milder symptoms. Batterman and Ehrenfeld (1949) found that smoking interferes with the medical management of peptic ulcer. In a group of 121 ulcer patients they found that smokers responded poorly to antacid therapy and had a higher incidence of acute exacerbations than non-smokers. Partially "denicotinized" cigarettes improved the response to treatment and a return to standard tobacco caused a relapse.

More cogent evidence has been produced by Doll, Avery Jones, and Pygott (1958). In a careful study, which should be consulted in the original paper, they found for gastric and duodenal ulcers in both sexes more smokers among ulcer patients than among controls. The number of heavy smokers did not differ appreciably in each group and the proportion who smoked cigarettes only was higher among both gastric and duodenal ulcer subjects than among controls. They did not think smoking con-

tributed directly to the production of ulcers because heavy smokers did not have a higher incidence of ulcer. They felt that either the presence of an ulcer might stimulate the desire to smoke or some psychological factor might predispose both to the development of an ulcer and to smoking. In a second study the same authors placed in-patient smokers with patients with gastric ulcers in two groups, one of which was advised to stop smoking. Otherwise management was the same. After four weeks the ulcers had healed significantly to a greater extent in the group advised to stop smoking. There was no difference in the amount of weight gain or in the severity of symptoms. It was concluded that in some patients smoking interferes with healing and helps to maintain chronicity. They thought that it was unlikely that tobacco was a direct cause of ulcer because tobacco consumption has increased in Great Britain in the past two or three decades whereas the incidence of gastric ulcer is thought to have diminished. In contrast, the incidence of duodenal ulcer has increased but its association with smoking is less. And the world distribution of mortality from peptic ulcer is quite unlike the distribution of smoking.

Hammond and Horn (1958) reported a follow-up of 187,783 men between the ages of 50 and 69. Regular cigarette smokers had the highest mortality in all age groups. A high association was found between regular smoking and death from carcinoma of the lung, larynx, and oesophagus, and from gastric ulcer. The association was not so high with death from duodenal ulcer. Of 51 deaths from gastric ulcer, 48 occurred in regular smokers and none in non-smokers; there was no evidence that this was due to associated respiratory disease. Doll and Hill (1956) recorded similar findings. Edwards, McKeown, and Whitfield (1959), in reviewing the smoking habits of 1,737 men over 60, found an increased incidence of peptic ulcer in smokers with a regular trend in prevalence according to the amount smoked.

Toon, Cross, and Wangensteen (1951) studied the effect of inhaling cigarette smoke in dogs with tracheotomies. Five cigarettes daily for six months produced no gastrointestinal lesion, but the same daily amount of smoke increased the ulcerogenic effect of daily injections of histamine in beeswax; the inhalation of more smoke in association with histamine gave a still higher incidence of ulcers while none were observed in control dogs. It was concluded that nicotine is the responsible agent because denicotinized smoke and histamine together cause few lesions. They also showed that in dogs cigarette smoke does not stimulate gastric secretion.

### Other Effects of Tobacco

Salivary Secretion.—Schnedorf and Ivy (1939) found that smoking increased salivary secretion in 15 chronic smokers and five non-smokers. This was probably a reflex change from mucosal irritation because 4 mg. of nicotine subcutaneously had no effect.

Carcinoma of Upper Alimentary Tract.—A number of papers record an association between smoking and carcinoma of the lip (Levin, Goldstein, and Gerhardt, 1950), carcinoma of the buccal and pharyngeal regions (Mills and Porter, 1950), and carcinoma of the oesophagus (Hammond and Horn, 1958).

Pancreatic and Biliary Secretion.—Few reports on this subject are available. It seems that neither smoking nor nicotine influence pancreatic or biliary secretions (Schnedorf and Ivy, 1939; Koehler, Hill, and Marsh, 1947).

The Colon.—Clinical observations suggest an association between smoking and colonic symptoms (Ryle, 1928; Bodley Scott, 1952). It has been shown in animals that nicotine applied on the floor of the fourth ventricle excites the activity of vomiting and defaecatory centres (Schnedorf and Ivy, 1939). These workers conducted a questionnaire addressed to 1,000 college students which revealed that 13·7% of males and 17·3% of females passed a greater number of stools after excessive smoking. When small groups of students were submitted to smoking and non-smoking periods of three days each it was found that the predominant effect of smoking was to increase the motor activity of the colon (Schnedorf and Ivy, 1939). Grace, Wolf, and Wolff (1951) found no evidence of a change in colonic motility in habitual smokers after one cigarette.

Malnutrition and Digestion.—There are surprisingly few reports in this connexion, despite the belief that smoking diminishes appetite and prevents weight gain. Koehler *et al.* (1947) observed the progress of six underweight patients who had reached their maximum weight on dietary measures. When they stopped smoking all gained between 7 and 14 lb. and the gain seemed to be due to improved appetite. Mitty, Rousselot, and Delany (1959) observed a large group of smokers and non-smokers after gastrectomy for ulcer. They found no correlation between smoking and the amount of weight loss after operation; nor did smokers have more significant digestive complaints than non-smokers. Smokers were, however, more liable to more major late complications such as recurrent ulcer.

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*Present-day Techniques*

# USE OF BISACODYL IN PREPARATION OF THE BOWELS FOR A BARIUM ENEMA

BY

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This account of a new and successful technique in preparing patients for a barium enema examination will interest clinicians, for its eventual adoption by radiologists would greatly reduce the discomfort of this invaluable but disagreeable investigation.

Half a century has elapsed since Rieder (1904) and Schüle (1904) first reported the use of opaque media for radiographic examination of the colon, during which time many other techniques have been improved. At the same time, whether due to medical prejudice or to the assertion of an exclusive nursing prerogative over the patient's bowels, methods of preparing the colon for the injection of barium do not appear to have shared in this process of general refinement. Nevertheless, a useful outcome from barium enema examination depends in no small measure upon this neglected aspect of technique.

Haenisch (1911) gave the first full review of the subject, and his exhaustive account includes the statement that "thorough cleansing of the intestine by giving purgatives and cleansing enemata is highly essential". Methods in general would appear to have changed little since his day. Various authorities (Sante, 1956; Storch, 1957) recommend a variety of measures, starting with dietary restriction of considerable austerity, and leading, via purgation with castor oil or phenolphthalein, to the administration of enemata of normal saline, soap and water, or, where gas is excessive, of ox bile and turpentine. Alternatively, plain water washouts may be given at half-hourly intervals until the fluid is returned clean. According to a standard British textbook (Shanks, 1958), the only satisfactory method of giving it is by means of the Studa chair in which 30-50 pints of fluid may have to be used before the return is clear.

Because the absence of an agreed standardized procedure makes it impossible to generalize, it is probable that the practice in most radiodiagnostic departments in this country closely resembles our own in relying largely on enemas and colonic lavage.

It was not until 1953 that a practical alternative to these methods became available. In that year the German pharmacologist Schmidt (1953) reported the synthesis of a new laxative substance now known as bisacodyl ("dulcolax"). This substance is not absorbed from the gut and is strikingly free from toxicity. Its presence within the lumen of the bowel initiates normal peristalsis due to direct contact with the mucosa, acting possibly through the local nerve plexuses. Clinical reports from Germany (Stockmeier, 1953; Frankl, 1953) confirmed its effectiveness in a variety of forms of constipation, and, since its widespread adoption in Britain, reports have appeared of its use in general medical and surgical cases (Church, 1959; Rutter, 1959) and in chronic sick and geriatric patients (Clark, 1957).

As a method of preparation for radiography, "dulcolax" suppositories were used by Hauff (1954) and Kolshorn (1954). The procedure used by these investigators consisted of either "dulcolax" tablets or a suppository on the evening before examination, and one suppository on the morning of examination, satisfactory bowel clearances being reported. Keogh and Fraser (1958) compared the effectiveness of bowel preparation in 100 patients prepared with castor oil and a cleansing enema and 142 patients given "dulcolax", and found that the "dulcolax" series gave better results. Good results were also obtained in a larger series of 249 patients prepared with bisacodyl (Poppel and Bangappa, 1959).

## Method of Investigation

In order to establish that it was possible to dispense with the enema and lavage commonly used in preparation for the barium enema, a "blind" enquiry was started in

this hospital in which the radiologists had to report on the adequacy of preparation at the time they read the films, without knowing what form of preparation had been used.

With the consent and cooperation of a number of medical and surgical consultants, patients referred for barium enema examination were allocated either to "old" or to "new" groups. Patients were allocated largely on the basis of the referring consultant, the ward sister being told that Mr. A's patients were to be given the "old" preparation and Dr. B's the "new", the method being such that no observable difference emerged in age, nature or severity of illness, etc., between the two groups of cases.

"OLD" METHOD OF PREPARATION

| | |
|---|---|
| Previous evening .. .. | One-and-a-half pint enema (4 oz. soft soap per pint) or disposable enema |
| 4 to 6 hr. before examination | Plain water lavage until clear |

"NEW" METHOD

| | |
|---|---|
| Previous evening .. .. | "Dulcolax", 10 mg. (2 tabs.) by mouth |
| 6 a.m. to 7 a.m. on morning before examination .. | One "dulcolax" suppository |
| One hour before examination | One "dulcolax" suppository |

As a rule the examination took place either at 11 a.m. or 1.30 p.m.

A note of the method used was made by the ward sister but did not appear on the form requesting a barium enema. When he had read the films the radiologist concerned was asked to complete a pro-forma stating whether preparation was "satisfactory" or "unsatisfactory", and, if the latter, for what reason and whether a diagnosis was still possible. The criteria used were as follows:—

*Unsatisfactory*
Faecal matter present in gross amount throughout colon, or failure to retain the enema

*Satisfactory*
Either empty of faeces, or faeces present in small amount insufficient to interfere with making a diagnosis

I was aware of the preparation used in each case but was not concerned with giving the initial opinion on the films. When the examination was over, the method of preparation used was entered on a pro-forma.

Two hundred cases were reviewed in this manner, 100 being given the "old" preparation and 100 the "new". The patients, who were all in-patients, included both sexes and all ages from 10 to 82 years. The majority were under investigation for suspected neoplasm or inflammatory lesions of the large bowel. Results are given in the accompanying table. Analysis showed that unsatisfactory results by either method bore no relation to age, sex, or to the ward which was preparing the enema. The patients marked "satisfactory" were later graded into "good" where there was no faecal residue at all in the colon, and "satisfactory" where minimal faecal matter was present in one segment of the colon only.

Side-effects in the "dulcolax" series were never serious but an occasional patient complained of colicky pain, nausea, or a burning sensation in the rectum after the suppository had been inserted. Our experience is that two tablets give an adequate result and a higher dose is inadvisable, particularly in the older age groups.

TABLE
RESULTS USING DIFFERENT METHODS OF PREPARATION FOR BARIUM ENEMA

| | No. of Patients Prepared by: | |
|---|---|---|
| | Routine Method | Dulcolax Method |
| Good (no gas or faeces in colon) | 62 | 73 |
| Satisfactory (small amount of gas or faeces in one segment of colon only) | 23 | 17 |
| Unsatisfactory: Due to faeces | 14 | 7 |
| Due to failure to retain enema | 1 | 3 |

*Since each group contained 100 patients, the figures may be read as percentages.

The relative lack of side-effects and the ease with which "dulcolax" is given make this preparation very suitable for the out-patient barium enema examination. Since the present series was completed many patients having a barium enema have been satisfactorily examined in this way.

## Discussion

The use of enemata and colonic lavage as a means of preparation for barium enema carries with it a number of disadvantages. In a proportion of cases the colon is not cleared or only partly so and residual gas or faeces may be troublesome. If the procedure is not carried out a sufficient length of time before the examination, droplets of fluid remaining in the colon may obscure the mucosal pattern, or the bowel may be irritated by the agents employed. A further important drawback is the risk of water intoxication to which attention has recently been drawn (*Lancet*, 1959). It is known that in susceptible cases absorption of hypotonic fluid can lead to neurological disturbances (Hiatt, 1951). Although most reported instances are in cases of megacolon, Ziskind and Gellis (1958) have shown that even in cases with a normal colon the volume of fluid returned after colonic lavage amounts to only 10 to 50% of that injected. When it is remembered that the procedure may involve the injection and return of 20 to 30 pints of water over the course of several hours, it becomes clear that an element of risk undoubtedly exists. Moreover, when the impact upon the patient, both physically and psychologically, of this "onslaught by water" is taken into account, many would doubt whether it can be justified at all except in the presence of clear and unequivocal indications.

Finally, the time expended by the nursing staff in administering the enema and lavage (at least half an hour), as well as in cleaning and maintaining the

equipment, makes the search for an alternative procedure an overdue medical obligation.

## Conclusion

The features of the ideal method of bowel preparation may be enumerated as follows:—

(1) It should produce complete and consistent bowel emptying within a predictable period of time.

(2) After emptying, the bowel should be left in an otherwise unaltered condition.

(3) From the patients' point of view the period of preparation should be short and the method should cause neither discomfort nor apprehension.

(4) From the nurses' point of view the method should be simple and quick.

(5) From the radiologists' point of view the procedure should result in a clear, unobstructed field of vision.

(6) There should be no side-effects or complications.

The conclusion to be drawn from this enquiry is that bisacodyl is an effective substitute for traditional methods of preparing the bowel and has the additional advantages of being simpler and quicker to administer and of being less unpleasant for the patient.

In view of the increasing use in hospitals of disposable enemata, it may be of interest to mention the following relative costs:—

| | Basic Cost to N.H.S. |
|---|---|
| Disposal enema | 1*s.* 8*d.* |
| Dulcolax régime (2 tabs. + 2 suppositories) | 7*d.* |

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# GASTRO-INTESTINAL BLOOD LOSS MEASURED BY RADIOACTIVE CHROMIUM

BY

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A new technique is described for the measurement of blood loss in the faeces of patients labelled with radioactive chromium ($^{51}Cr$). The method is simple and is probably more accurate at low levels of faecal radioactivity than those previously described. The method will measure as little as 0·02$\mu$C of $^{51}Cr$ in whole blood in a 24-hour stool.

The apparent average daily blood loss in a series of 10 normal people averaged 0·6 ml., with a range of 0·3 to 1·3 ml.

Estimations of plasma and salivary radioactivity have been made in an attempt to assess the importance of contamination from eluted $^{51}Cr$. Minor radioactivity in plasma but none in saliva was recorded. Stool contamination from such sources is thought to be insignificant.

No significant correlation existed between chemical occult blood tests and isotope measurements, where there was less than 10 ml. of whole blood in a 24-hour stool.

*In receipt of a Medical Research Council grant.

Since the turn of the century numerous chemical tests, of varying sensitivity, have been available for the detection of occult blood in the stools, but it is only in the last 10 years that methods have become available for its precise measurement.

The isotope of chromium, $^{51}Cr$, when prepared as $Na_2\,^{51}CrO_4$, has proved a satisfactory label for measuring the survival time of human red cells. Owen, Bollman, and Grindlay (1954) showed that it could be used to measure the quantity of blood passed in the faeces of dogs. Their methods have been applied to man by Roche, Perez-Gimenez, Layrisse, and Di Prisco (1957), Ebaugh, Clemens, Rodnan, and Peterson (1958), and Bannerman (1957). All these workers calculate the amount of blood in the faeces by measuring the radioactivity in a weighed aliquot representing 3-4% of a fluid homogenate of the stool. The method is both malodorous and cumbersome. Hughes Jones (1958) compared this rather tedious technique with that described by Booth and Mollin (1956) in which the radioactivity of the whole stool in its collection carton is measured in a ring counter containing 32 Geiger-Muller tubes in parallel. Unfortunately this simple method did not prove very sensitive. Sensitivity is improved by the use of the turret type counter in which the collection carton is placed between two scintillation crystals sensitive to $\gamma$ rays. This equipment is very expensive, and has the disadvantage that the stool is not completely surrounded by the crystal, thus reducing its sensitivity at low levels of faecal radioactivity; furthermore, considerable care has to be taken to position the stool at the geometric centre of the counter (Lewis, 1959).

The purpose of the present communication is to describe a simple, inexpensive, relatively odourless technique which is sensitive at low levels of faecal radioactivity. The daily blood loss has been measured by this method in normal adults. The possibility of reabsorption of $^{51}Cr$ from the gut and of leakage of eluted $^{51}Cr$ from the plasma has been investigated. The daily blood loss has also been measured in patients with positive chemical tests for occult blood and the results compared.

## Methods

A. Technique for Labelling Blood with $^{51}Cr$.—The patient's cells are labelled with $^{51}Cr$, using the method described by Mollison and Veall (1955). About 20 ml. of venous blood is withdrawn into a sterile universal container, containing 5 ml. of acid citrate dextrose solution. The sample is then centrifuged and the supernatant plasma removed. Approximately 100 $\mu$C of $Na_2\,^{51}CrO_4$ with a specific activity of 10 to 30$\mu$C per mg. of chromium is added to the cells, with rapid and thorough mixing, to ensure an even coating of chromium over the cells. The suspension is then allowed to stand for 30 minutes at room temperature, and is gently rotated every five minutes. The packed cells are then washed three times in sterile saline, and are then resuspended in saline to a volume of approximately 25 ml. By means of a U-shaped needle (Lewis, 1959), 20 ml. is carefully withdrawn into a calibrated syringe and injected intravenously into the patient. Blood samples are taken from the patient 15 minutes later, after 24 hours, and subsequently every three days. The samples are haemolysed by the addition of a knife point of "saponin". Samples, each of 3 ml., are counted, and after correction for background their radioactivity can be plotted. The dosage of administered radioactivity is calculated by the use of a standard prepared from the residue of the original saline suspension of red cells diluted 100 times in water.

B. Collection and Preparation of Faecal Samples.—Because of the relatively long half life—27·8 days—of $^{51}Cr$, each patient can be studied for four to six weeks after his red cells have been labelled. All stools passed during the period of investigation are collected in successive numbered cartons. Each stool is passed onto a square of cellophane paper placed in a bed pan under a portable commode. The cellophane-wrapped stool is then transferred to a 20-oz. waxed screw-topped carton. In the laboratory a small faecal sample is removed for chemical occult blood estimation. The stool is then dried in an electric oven, thermostatically controlled at 170°F. so that spattering does not occur; drying takes about 15 hours. The odour is eliminated by housing the oven in a fume cupboard containing an extractor fan.

The dried stool is then placed in a glazed glass mortar, the cellophane ashed by ignition, and the whole ground to a fine powder. Thorough mixing occurs during the grinding process. The powdered stool is weighed and a 10 g. aliquot packed in glass test tubes and counted in a well-type scintillation crystal. The aliquot averages 20% of a normal dried stool, and is packed into three or four tubes, so that each tube contains about 3 ml. of ground stool which is the optimal volume for the counter.

C. Measurement of Radioactivity.—The most convenient and sensitive method for estimating the faecal radioactivity is by the gamma ray emission from $^{51}Cr$ measured in a well-type thallium-activated sodium iodide crystal. An "echo" scintillation counter type N.550A was used in these experiments. A minimum of 2,500 counts was made so that the coefficient of variation was about 2%. The recorded activity of the faecal aliquot was corrected for background, and the blood content of the 24-hour faecal collection calculated from the formula:—

$$\frac{\text{Total C.P.M. in aliquot}}{\text{C.P.M./ml. of venous blood standard}} \times \frac{\text{Wt. of 24-hr. stool}}{\text{Wt. of aliquot}}$$

Because it is impossible to measure accurately intestinal transit time the blood samples used as the standards in the formula were those taken two or three days before passage of the stool.

## Results

PERCENTAGE RECOVERY OF INGESTED $^{51}$Cr-LABELLED RED CELLS.—Labelled red cells, 1-5 ml., containing 0·02 to 0·03 microcuries/ml. of $^{51}$Cr, were given orally in a gelatin capsule to 10 patients, none of whom had previously received any radioactive blood. An average of 97·4% of the administered blood was recovered in faecal collections over the succeeding five days. This suggests that loss of $^{51}$Cr by absorption from the alimentary canal does not constitute an important source of error in the method. It also shows that drying the stools at 170°F. does not apparently lead to any significant loss of radioactivity.

The results are shown in Table I.

TABLE I

PERCENTAGE RECOVERY OF INGESTED $^{51}$Cr-LABELLED BLOOD

| Case | Sex | Age | Blood Ingested (ml.) | Blood Recovered from Four-day Collection (ml.) | % Recovery |
|---|---|---|---|---|---|
| 1 | F | 65 | 1 | 0·9 | 90 |
| 2 | M | 47 | 1 | 1·02 | 102 |
| 3 | M | 32 | 1 | 1·04 | 104 |
| 4 | M | 43 | 2 | 2·18 | 109 |
| 5 | M | 34 | 2 | 1·92 | 95 |
| 6 | F | 24 | 2 | 2·1 | 105 |
| 7 | M | 43 | 3 | 2·7 | 90 |
| 8 | M | 34 | 3 | 2·8 | 93 |
| 9 | M | 34 | 5 | 4·6 | 92 |
| 10 | F | 24 | 5 | 4·7 | 94 |

Mean = 97·4%, S.D. = ± 6·6, S.E. = 1·9.

VALIDITY OF RESULTS OBTAINED FROM A 10G. ALIQUOT.—To test the validity of results obtained from a 10 g. aliquot, stools were collected from six patients who were on a small dose of aspirin and whose red cells had been labelled with $^{51}$Cr. The radioactivity in the whole of each stool was measured, after drying and powdering. An aliquot of 10 g. was then taken from each stool and counted and the total radioactivity was calculated. Table II compares the results obtained by counting the whole stool with the results obtained from a 10 g. aliquot, and shows that the aliquot technique is both reliable and satisfactory.

TABLE II

RECOVERY FROM TOTAL STOOL COUNT WITH ESTIMATED RECOVERY FROM 10g. ALIQUOT COMPARED

| Case | Sex | Age | Blood Recovered from Whole Stool (ml.) | Blood Estimated from 10g. Aliquot (ml.) | % Recovery by Aliquot Method |
|---|---|---|---|---|---|
| 1 | M | 72 | 3·7 | 3·9 | 105·5 |
| | | | | 3·8 | 102·5 |
| 2 | M | 73 | 3·5 | 3·6 | 102·5 |
| | | | | 3·5 | 100·0 |
| 3 | M | 70 | 4·7 | 4·7 | 100·0 |
| 4 | M | 19 | 2·3 | 2·3 | 100·0 |
| 5 | M | 70 | 2·6 | 2·6 | 100·0 |
| 6 | M | 19 | 7·6 | 7·8 | 102·5 |

Mean = 101·6%, S.D. = ± 1·99, S.E. = 0·7.

APPARENT AVERAGE DAILY BLOOD LOSS IN NORMAL ADULTS.—The apparent average daily blood loss was investigated in 10 patients who had no known gastro-intestinal disease and negative occult blood reactions both to the benzidine and "haematest" reaction. The radioactivity in 60 stools was measured after intravenous administration of labelled R.B.C.s. The results in Table III show an average daily blood loss of 0·6 ml. with a range from 0·3 ml. to 1·3 ml.

PLASMA RADIOACTIVITY DUE TO ELUTED $^{51}$Cr.—It is not known for certain that the $^{51}$Cr in stools represents $^{51}$Cr-labelled red cells only, and it has been suggested that a proportion might be due to eluted $^{51}$Cr excreted into the gut. It is because of this uncertainty that the figure for normal daily blood loss has been expressed as "apparent" normal daily loss. In order to assess the level of radioactivity in the plasma due to eluted $^{51}$Cr, 30 patients

TABLE III

AVERAGE DAILY BLOOD LOSS IN STOOLS IN NORMAL SUBJECTS TAGGED WITH $^{51}$Cr

| No. of Case and Diagnosis | Age | Sex | Days Stools Collected after Labelling with $^{51}$Cr | No. of Stools | Apparent Average Blood Loss (ml./day) |
|---|---|---|---|---|---|
| 1. Normal | 19 | F | 1 to 15 | 15 | 0·3 |
| 2. Sideroblastic anaemia | 58 | M | 12 to 16 | 4 | 0·5 |
| | | | 20 to 23 | 3 | 0·6 |
| 3. Hypochromic anaemia | 70 | F | 1 to 5 | 5 | 1·2 |
| 4. Pulmonary tuberculosis | 25 | F | 1 to 3 | 3 | 0·3 |
| 5. Diabetes | 72 | M | 1 to 4 | 4 | 1·3 |
| | | | 16 to 18 | 3 | 0·6 |
| 6. Normal | 44 | M | 1 to 7 | 7 | 1·0 |
| 7. Pulmonary tuberculosis | 58 | M | 1 to 4 | 4 | 0·3 |
| 8. Pulmonary tuberculosis | 51 | M | 1 to 3 | 3 | 0·3 |
| 9. Arteriosclerosis | 70 | M | 1 to 3 | 3 | 0·5 |
| 10. Cholelithiasis | 45 | F | 1 to 3 | 3 | 0·7 |

Mean = 0·6 ml., S.D. = ± ·35 ml., S.E. = 0·1 ml.

TABLE IV

PLASMA LEVEL OF RADIOACTIVITY AS % OF RED CELL RADIOACTIVITY

| No. of Patients | Time of Measurement after Tagging | Mean Plasma Level of Radioactivity (%) |
|---|---|---|
| 9 | First 24 hours | 0·28<br>Range 0 - 0·5 |
| 21 | Between one and four weeks | 0·3<br>Range 0·08-0·45 |

labelled with $Na_2{}^{51}CrO_4$ were investigated. The results are expressed in Table IV. In nine patients blood samples were taken during the first 24-hour period after labelling. The blood was centrifuged and the radioactivity in 3 ml. of the supernatant plasma measured and compared with the radioactivity in 3 ml. of red cells. In a further 21 patients plasma activities were measured from one to four weeks after labelling. The mean result of plasma activity, expressed as a percentage of the red cell activity measured at the same time, was 0·28% in the first 24 hours and 0·3% in any sample taken during a subsequent period.

RADIOACTIVITY OF SALIVA DUE TO ELUTED $^{51}Cr$.—The radioactivity of the saliva was measured in 10 patients labelled with $^{51}Cr$. Measurements were made during the first 24 hours and at subsequent intervals over the course of four weeks, but in no case was the background count exceeded.

COMPARISON WITH CHEMICAL TESTS FOR OCCULT BLOOD.—The volume of blood was measured in 500 stools from 25 patients, and compared with the results of testing for occult blood by the benzidine and "haematest" methods. The benzidine test was performed using the method of Needham and Simpson (1952), and the criteria accepted were:—

Strong positive (+++) was taken as the immediate appearance of a deep blue colour.

Positive (++) was taken as a deep blue colour appearing within 15 sec.

Weak positive (+) was taken as a blue colour appearing within 30 sec.

Any colour appearing after this period was expressed as a negative (−).

The "haematest" method was performed according to the manufacturers' instructions.

A positive (+) result was taken as a deep blue staining on the test paper appearing within two minutes, otherwise a negative (−) result was recorded. The active ingredients of the "haematest" tablet are O-toluidine, strontium peroxide, calcium acetate, and tartaric acid.

Table V shows the results found in 10 consecutive stools passed by three patients who were taking a small dose of aspirin. The poor correlation shown in this small sample is typical of the whole series of 500 stools tested from 25 patients.

## DISCUSSION

The sensitivity of the method described in this communication is shown by the recovery in a 24-hour stool of as little as 0·02 $\mu$C of ingested $^{51}Cr$ contained in 1 ml. of whole blood. The average dried stool weighs about 40-50 g. and the whole can easily be counted but the stool is mixed so thoroughly by drying and powdering that it is unnecessary to count more than a 10 g. aliquot, representing 20%. By contrast the more usual method involves diluting the stool, homogenising and weighing it, and then measuring an aliquot which only represents about 2%, a malodorous and rather cumbersome process. By the use of this technique Bannerman (1957) was able to measure accurately only amounts of 3 ml. or more. The results of Ebaugh *et al.* (1958) and Hughes Jones (1958) suggest greater sensitivity, but their precise accuracy is difficult to determine because the dose of $^{51}Cr$ given and the volume of blood containing it was so large.

The recovery of 97·4% of relatively small orally administered doses of $^{51}Cr$-labelled red cells suggests

TABLE V

CHEMICAL ESTIMATION OF OCCULT BLOOD COMPARED WITH RADIOACTIVITY MEASURED IN STOOLS OF THREE PATIENTS ON SMALL DOSE OF ASPIRIN

| Case 1.—Male aged 56 | | | Case 2.—Male aged 59 | | | Case 3.—Male aged 75 | | |
|---|---|---|---|---|---|---|---|---|
| Benzidine Test | Haematest | Measured Blood Loss (ml.) | Benzidine Test | Haematest | Measured Blood Loss (ml.) | Benzidine Test | Haematest | Measured Blood Loss (ml.) |
| ++ | + | 1·9 | +++ | — | 4·2 | + | + | 1·2 |
| — | + | 3·9 | +++ | — | 0·7 | ++ | + | 1·1 |
| + | + | 2·8 | +++ | + | 3·4 | + | — | 3·7 |
| ++ | + | 11·1 | ++ | + | 2·1 | + | + | 1·5 |
| ++ | + | 2·3 | +++ | + | 0·3 | + | — | 3·5 |
| + | — | 2·9 | +++ | + | 5·2 | + | — | 0·6 |
| + | — | 0·6 | +++ | + | 6·8 | + | — | 1·9 |
| + | — | 0·9 | +++ | + | 10·6 | + | — | 3·4 |
| +++ | — | 3·8 | +++ | — | 9·5 | + | + | 4·2 |
| ++ | — | 1·2 | ++ | + | 5·5 | ++ | + | 9·9 |

that apparently hardly any of the $^{51}Cr$ is absorbed from the gut, and thus agrees with the results of Owen *et al.* (1954), Roche *et al.* (1957), and Ebaugh *et al.* (1958). Hughes Jones (1958) gave oral doses of 21 $\mu$C of $^{51}Cr$ and 8 $\mu$C to two patients, and was only able to recover 66% and 87% of the administered dose. He concluded that it seemed reasonably certain that the discrepancy was due to reabsorption of some of the $^{51}Cr$ by the gut. This assumption seems unlikely because both Roche *et al.* (1957) and Ebaugh (1958) could recover less than 0·5% of the $^{51}Cr$ from the urine, and found less than 0·2% of the ingested $^{51}Cr$ to be present in the circulating blood.

The apparent average daily loss in normal people of 0·6 ml. of whole blood was found. A similar figure was obtained by Hughes Jones (1958), and Levin, Hart, and Bothwell (1959) but is rather less than the quantity found by Roche *et al.* (1957) and Ebaugh *et al.* (1958), namely 1·2 ml. It has been suggested that this difference may be due to the fact that these authors did not remove the unattached $^{51}Cr$ by washing their cells after labelling (Hughes Jones, 1958). It has been shown by Owen *et al.* (1954) in dogs, and by Roche *et al.* (1957) in man, that the greater proportion of chromium separated from the red cells and present in the plasma is excreted rapidly by the kidneys. Roche *et al.* (1957) found that after intravenous injection of labelled red cells 96·3% of the total daily recovery of radioactivity was in the urine. Mollison and Veall (1955) have shown that after the intravenous administration of labelled red cells, most of the chromium attached to senile cells or poorly bound to the cells is eluted within the first 24 hours. Hughes Jones and Mollison (1956) further estimated that thereafter the rate of elution is steady. If any significant amount of eluted chromium were to diffuse into the alimentary canal this should occur in the first 24 hours after injection. No evidence in support of this possibility has been found. There was no significant increase in faecal radioactivity in the first 48-hour stool samples as compared with later specimens. Previous workers in this field have given no figures of plasma radioactivity; such estimations were made and compared with the red cell radioactivity during the first 24-hour period and subsequently at intervals during the course of a four-week investigation and at no time was significant activity recorded. In the present series, in conformity with standard practice, the red cells were labelled with hexavalent $Na_2{}^{51}CrO_4$ which is thought not to cross the intestinal barrier, Owen *et al.* (1954) having shown that small quantities of the trivalent ion can pass through the gut wall. If, as has been shown (Roche *et al.*, 1957), most of the chromium eluted from the labelled red cells is excreted by the kidneys, it is highly probable that very little $^{51}Cr$ can diffuse through the bowel wall.

Radioactivity in the saliva of patients labelled with $^{51}Cr$ was measured, but in no case was the background count exceeded. These results go some way to discount the suggestion that eluted $^{51}Cr$ might be stored and excreted into the intestine by an active glandular process.

It is therefore concluded that in patients labelled with well-washed hexavalent chromium-tagged red cells, the radioactivity in a 24-hour stool represents red cell loss into the intestine, and that contamination by eluted $^{51}Cr$ is insignificant. It is more likely that minor contamination by eluted chromium could occur from bile. Owen *et al.* (1954) have shown in dogs, but not in humans, that a small quantity of chromium is excreted in bile.

Great diversity of opinion has always existed about the usefulness of chemical occult blood tests as a quantitative measure of minimal faecal blood loss. Needham and Simpson (1952), using *in vitro* methods, have shown that a modification of the benzidine test would give a positive result with as little as 3 ml. of blood. Bannerman (1957), however, found little correlation between the benzidine test and isotope measurements when small quantities of blood were in question. The benzidine test has now been withdrawn because of carcinogenic risks incurred in its manufacture, and reliance has now been placed on O-toluidine as a chemical agent sensitive to occult blood. In the present experiments such variation was found between the results of the chemical tests in 500 stools containing less than 10 ml. of blood estimated radioactively that the only permissible conclusion which could be drawn was that these chemical tests possess some value as screening procedures but are useless as a quantitative measurement of alimentary bleeding. It is appreciated that the poor correlation between the radioactive measurement of occult blood and the chemical tests (particularly the "haematest" method) is partly due to sampling errors. False negative results can be obtained from incomplete mixing of blood in the stool which frequently occurs in patients who are bleeding intermittently. False positive results have always been the drawback of chemical tests which are too sensitive. Such false positive results are shown in Case 2 (Table V). It is thus extremely difficult to find a standard chemical test which is neither too sensitive nor too insensitive. It is therefore recommended that in order to minimize sampling errors the "haematest" method should be duplicated on each specimen.

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# THE MARCH (1960) ISSUE

The March (1960) issue contains the following papers:—

Foreword. HAROLD C. EDWARDS.

History of the British Society of Gastroenterology. THOMAS HUNT.

Early Investigations of Haematemesis. G. N. CHANDLER, A. D. CAMERON, A. H. NUNN, and D. F. STREET.

The Incidence of Chronic Peptic Ulcer Found at Necropsy. GEOFFREY WATKINSON.

Observations on Blood Group Distribution in Peptic Ulcer and Gastric Cancer. R. DOLL, B. F. SWYNNERTON, and A. C. NEWELL.

The Effects of Corticotrophin and Corticoids on Secretion from Denervated Gastric Pouches in Dogs. S. D. CLARKE, D. W. NEILL, and R. B. WELBOURN.

Serotonin, Bananas, and Diarrhoea. A. M. CONNELL, E. N. ROWLANDS, and P. B. WILCOX.

Coeliac Disease: Histopathological Findings in the Small Intestinal Mucosa Studied by a Peroral Biopsy Technique. MARGOT SHINER.

A Study of the Pancreatic Response to Food after Gastrectomy in Man. T. J. BUTLER.

Intestinal Pseudo-obstruction with Steatorrhoea. J. M. NAISH, W. M. CAPPER, and N. J. BROWN.

Diagnostic Significance of d.Xylose Excretion Test. D. FOWLER and W. T. COOKE.

Multiple Endocrine Adenoma Syndrome. W. T. COOKE, D. I. FOWLER, R. GADDIE, E. V. COX, M. J. MEYNELL, and D. BREWER.

Volvulus of the Small Intestine in Adults. C. H. TALBOT.

Annual Meeting of the British Society of Gastroenterology.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

*Gut*, 1960, **1**, 183.

# POST-GASTRECTOMY SYNDROMES: A REVIEW

BY

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Arthur Hurst many years ago enunciated the aphorism "gastro-enterostomy, a disease". He might with much greater justice have scoffed at gastrectomy which, though it eliminates the ulcer, too often creates its own peculiar aftermath of afflictions. Hurst did indeed anticipate our present problem, for in 1913, writing on the unfavourable effects of gastroenterostomy, he described one clear case of what we now call the "dumping syndrome", and moreover he recognized it to be the result of too rapid drainage of the stomach.

The term "dumping" seems to have been applied first by Dr. C. H. Mix, a Chicago surgeon, in a paper entitled "Dumping stomach following gastro-jejunostomy", which was published in 1922. His case was a woman aged 40, referred to him by a physician "who was doing the best he could but that was little because her needs were great". Mix carried out an *x*-ray examination and reported that the bismuth slipped out of the stomach almost as fast as it entered. He drew the conclusion that "Nature never intended to have the stomach connected up with the intestine, just any place". Nature has, alas, been thwarted many times since then, and examples of the post-gastrectomy syndromes now bulk large among the return cases of every surgeon engaged in this field.

There is general agreement that all the various disturbances under consideration are due to the precipitate unloading of food from the stomach into the small intestine. However, the disturbances take different forms in different patients and it is convenient to describe four distinct syndromes, though sometimes they occur together in greater or less degree, namely, (1) the early post-prandial (post-cibal) syndrome, (2) bilious vomiting, (3) the late post-prandial or hypoglycaemic syndrome, and (4) the malabsorption syndrome.

The term "dumping syndrome" should logically be applied to all these conditions but is usually restricted to the early post-prandial syndrome. Many writers have regarded bilious vomiting as merely one component of the post-prandial syndrome, and indeed they sometimes occur together. However, most patients with post-prandial symptoms do not vomit, and most patients with bilious vomiting have relatively little post-prandial trouble. Moreover, they may arise from different causes and certainly they respond to different types of operative treatment, so they are best discussed separately.

## The Early Post-prandial Syndrome

This syndrome develops during or shortly after a meal and is characterized by epigastric distension and discomfort with muscular weakness, drowsiness, and faintness. It persists for half an hour or so and then passes off completely until the next meal. In some cases the relief of symptoms is marked by vomiting of a few ounces of pure bile or the passage of a copious soft stool.

The most notable feature is the feeling of extreme weakness. In the mildest cases the patient when walking or standing after a meal feels light headed, almost as though intoxicated, and a little unsteady in his gait. In more severe cases the limbs feel heavy and weak and there is a compelling urge to lie down. There many be transitory fainting or black out. Sometimes there is a sensation of heat throughout the body with flushing or perhaps a cold sweat. During the attack the pulse rate may rise. The blood pressure may rise or fall.

The early post-prandial syndrome generally appears a few weeks after operation, when the patient is becoming more active and taking larger meals. At that phase it probably occurs in greater or less degree in the majority of gastrectomy cases. During succeeding months the symptoms tend to improve but in a hard core of cases they persist in a disabling form. Occasionally post-prandial symptoms arise for the first time several months or even years after the operation.

Frequency and Incidence.—In my own series, as reported recently by Duthie (1960), post-prandial symptoms of some sort or other occurred at some time during the post-operative course in nearly 80% of cases. The commonest feature was epigastric fulness, but as a rule it was of slight degree

and caused little disturbance. On the other hand the vasomotor symptoms, which occurred in 47% of cases, caused a good deal of disability and in their more severe forms they could be incapacitating for patients engaged in active occupations. Fortunately, in the majority the symptoms were not severe—even at the worst they tended to be regarded as an improvement on the pre-operative ulcer pain—and they tended to diminish in severity in the course of six months or a year. However, at the end of six years there remained a hard core of 9·4% patients in whom severe symptoms persisted.

The Polya type of operation (gastrectomy with gastrojejunal anastomosis) and its various modifications are the procedures most likely to cause trouble, but post-prandial symptoms may occur also after the Billroth I operation (gastrectomy with gastroduodenal anastomosis) and even, rarely, after gastrojejunostomy. It is not known whether the additional step of vagotomy has any significant effect. Study of the literature, which has been reviewed recently by Capper and Welbourn (1955), makes it clear that there is marked diversity of opinion as to the frequency with which the syndromes develop in patients of various clinical types, and also a diversity of opinion as to the effect of different types of operative technique.

There is probably no sex difference. Some writers have found women twice as liable as men, but in my own series the reverse was the case. Nor is there any clear evidence as to whether patients treated originally for gastric ulcer differ from those treated for duodenal ulcer. It is said that patients who have had long-standing severe pain before operation are less liable to post-operative trouble but this is probably because they are more willing to tolerate what they regard as a comparatively trifling disability.

As regards the precise technique of operation, most writers are agreed that the risk of dumping is greatest in those cases where a large amount of stomach has been removed and in those where the stoma is of large size, in other words, where rapid unloading is most likely to occur. There are diverse opinions but little tangible evidence as to the relative liability of cases with antecolic or retrocolic anastomosis or between left-to-right and right-to-left arrangement of the jejunal loop.

PATHOLOGY.—Every surgeon with experience of operating on cases with severe post-prandial symptoms must have been impressed by the paucity of the pathological changes within the abdomen. The stoma itself rarely presents any abnormality of note. Changes have been described affecting the afferent loop—fixation, scarring, partial obstruction, dilatation—but they are probably due to technical defects in the performance of the gastrectomy and are certainly not present in many patients with severe symptoms. In my own experience it is rare to find any recognizable abnormality of the afferent jejunal loop.

Only the efferent loop presents pathological changes and they are constant and characteristic. This part of the jejunum is somewhat enlarged, perhaps to twice its normal diameter, thick-walled, vascular, congested, heavy with blood. There is no obstruction twisting, or kinking. Distally, these changes extend for perhaps 8 or 10 in. and then gradually diminish. It cannot be doubted that they are the result of irritation by food unloaded precipitately from the stomach. They provide an index of the stress to which this part of the small intestine is subjected after gastrectomy and make it easy to understand how motor excitability, stasis of blood, and osmotic fluid shift may occur in this area after a meal.

METHODS OF INVESTIGATION.—One of the difficulties in finding the cause of the post-prandial symptoms arises from the fact that, like most subjective impressions, they are fickle in occurrence and very liable to be modified or obscured by incidental conditions. For example, the symptoms subside quickly when the patient lies down; if he takes his meals in bed the symptoms do not develop. A patient who gives a history of severe symptoms occurring almost without relief since the time of the gastrectomy may not produce a single symptom if he is admitted to hospital for investigation. This fickleness of occurrence has led some observers to suspect a psychosomatic factor, but it is quite possible that the relief on admission to hospital is due to the diminished bowel motility which every patient experiences during his first few days in hospital.

In order to provoke post-prandial symptoms for the purposes of investigation it is customary to give hypotonic glucose solution by mouth, the usual dose being 100 or 150 ml. of 50% glucose in water flavoured with lemon. Such a meal brings on an attack with fair regularity in a patient liable to the spontaneous attacks provided he remains sitting or standing. It must be remembered, however, that attacks may follow a meal containing no glucose, so the biochemical changes following a glucose meal may not necessarily be essential features of the spontaneous syndrome.

AETIOLOGY OF THE EARLY POST-PRANDIAL SYNDROME.—It seems probable that the two components of the early post-prandial syndrome, the epigastric

distress and the vasomotor features, are brought about in different ways.

The epigastric fulness and discomfort are almost certainly related to motor disturbance in the small intestine. The vasomotor symptoms have been attributed to a number of different causes, including blood sugar changes, sympathetic stimulation, potassium loss, and falling plasma volume.

There is no doubt that all these processes can occur, but their occurrence is not limited to patients with symptoms, and many workers have expressed the view that they occur just as often and in just as marked a form in patients who are symptom free. For this reason their importance as the cause of the syndrome remains in doubt.

*Intestinal Motility.*—Many radiological studies have shown that after gastrectomy the stomach empties rapidly and transmission of the meal through the small intestine also is usually very rapid. Sometimes also the meal is transmitted rapidly through the colon.

One of the most recent and most complete of such radiological studies is that by Duthie and McKellar (1960). They examined 29 cases after Polya gastrectomy, using a non-flocculating barium sulphate micro-suspension to which was added 75 g. glucose. They confirmed that the stomach remnant nearly always empties very rapidly. In 20 cases it was empty within 10 minutes. Small intestine hypermotility was evident on screening when the bowel was seen writhing and twisting as the opaque meal passed rapidly to the colon. The time taken for the head of the meal to reach the caecum in about half the cases was 20 minutes or less; in one case the caecum was reached in six minutes. Hypermotility of the colon was also seen, though less frequently.

Another feature, described by several previous workers, is a lack of definition of the small bowel. The mucous pattern is blurred and sometimes small fluid levels are seen. This picture is attributed to dilution of the barium suspension by an excess of fluid, doubtless an osmotic shift of water in response to the hypertonic glucose. There is little doubt that this excess of fluid is an important cause of the hypermotility.

The motility pattern of the small intestine has also been examined by the use of inflatable balloons connected with the kymograph. Glazebrook and Welbourn (1952) made observations by this means, the balloon being introduced through the stomach into the efferent loop of jejunum. They confirmed that after gastrectomy the small intestine shows a great deal of motor activity and in particular there are numerous rapid-frequency waves of contraction similar to normal segmentation waves.

There seems good reason to accept the view that these motility changes are responsible, at least in part, for the epigastric fulness and distress which occur soon after a meal. Possibly the aching heaviness described by many patients is due in part also to vascular congestion of the afferent loop of jejunum.

A few workers have suggested that the intestinal hypermotility is also responsible for the vasomotor features of the early post-prandial syndrome, perhaps by initiating a reflex action and liberating a vasoconstrictor substance such as adrenaline. In support of this view Liljedahl, Mattsson, Pernow, and Wallensten (1959), who studied the small intestine by ciné radiography, claim that peristalsis is livelier in patients with vasomotor symptoms than in those who are symptom free. Duthie and McKellar, on the other hand, could find little difference either in the rate of gastric emptying or the time taken for the meal to reach the caecum, though they noted that hypermotility of the colon was more marked in the group with symptoms. Incidentally, Duthie and McKellar noted that the hypermotility persisted when the patient was put in a supine position, although vasomotor symptoms did not then develop.

*Blood Sugar Changes.*—It has been known for many years that after gastrectomy, both in patients with symptoms and in those without symptoms, the blood sugar level is subject to wide fluctuations.

Lapp and Dibold in 1933 found that in patients after gastric operations when glucose was given by mouth there was an abrupt rise in blood sugar to an abnormally high level, followed by a sharp fall to within the hypoglycaemic range. They noted also that comparable changes could be produced in normal subjects giving the glucose through a tube directly into the jejunum. Similar findings have been reported by many writers since that time.

There is, of course, a good deal of individual variation, and in some gastrectomy cases the results of the glucose tolerance test lie within the normal range. More commonly, however, the blood sugar at 30 min. or 45 min. will rise to above 150 mg. per 100 ml. and it may rise to 250 or even to over 300 mg. It tends to maintain this high level for an hour or more and then falls abruptly to 50 mg. or lower.

The customary explanation of the early rapid rise of blood sugar is that it is due to unduly rapid absorption from the jejunum consequent on the precipitate gastric emptying. Indeed, Smith and his colleagues have used the rate of sugar elevation as an index of the rate of gastric emptying. It is possible, however, that some part of the rise in blood sugar may be due to the action of adrenaline, or

perhaps due to faulty utilization of the circulating sugar.

The conditions governing the late hypoglycaemic phase will be considered later, in connexion with the syndrome which occurs at that time.

It has long been known that the early post-prandial syndrome is not related to hypoglycaemia, which occurs much later. The early syndrome develops precisely at the time when the early rise in the level of the blood sugar is beginning to make its appearance. Glaessner (1940), who was the first to draw attention to this coincidence, attributed the symptoms to "hyperglycaemic shock", and other writers since that time have attempted to relate the two phenomena, either directly or indirectly. There is, however, a good deal of evidence against this view.

The blood sugar changes occur in gastrectomy patients who are without symptoms as well as in those with post-prandial symptoms, and there is diverse evidence as to whether the sugar changes are greater in the one group than the other.

Smith, Fraser, Staynes, and Willcox (1953), in an investigation of 26 patients subjected to gastrectomy after various types of meal, found a definite correlation between the steepness and extent of the rise in blood sugar and the severity of the symptoms; on the other hand, most other workers have been unable to confirm this finding. In my own unit, Duthie (1959), who made a study of 40 cases after Polya gastrectomy, found that the mean blood sugar levels in 20 patients with vasomotor symptoms were no different from those in the 20 who were symptom free. Nor was there any difference in the rate of rise of the blood sugar. In his series also there was no correlation between the blood sugar rise and either the fall of plasma volume or the electrocardiographic changes.

It is perhaps even more informative to study in detail individual records of blood sugar levels and to compare them with the severity of the symptoms with which they were associated. The paper by Schechter and Necheles (1949) is convincing in this respect. These workers studied 11 cases after administering 100 g. glucose in 3% solution by the mouth. Four of these patients showed no undue degree of elevation of the blood sugar yet they developed vasomotor symptoms, of moderate severity in three, severe in the remaining one. Two of the patients showed marked hyperglycaemia yet remained symptom free.

Perhaps the most emphatic evidence against hyperglycaemia as the cause of the early post-prandial symptoms is provided by two complementary types of observation. It has been shown (Schechter and Necheles, 1949; Duthie, 1959) that hyperglycaemia of comparable degree produced by infusing glucose intravenously causes no symptoms. And it has also been shown that typical early post-prandial symptoms can be produced by manoeuvres which cause no hyperglycaemia, for example, by giving laevulose (Schechter and Necheles) or mannitol (Duthie, 1960) which are absorbed and metabolized too slowly to affect the blood glucose level, or by giving a protein meal (Borgström, 1957), and even by distending the jejunum with a balloon (Machella, 1950; Glazebrook and Welbourn, 1952).

*Sympathetic Stimulation.*—Irvine in 1948 in a study of 24 cases noted that the early post-prandial symptoms are related to the bulk of a meal rather than to its content of glucose and supported the view that distension of the gut might be responsible by initiating a nervous reflex. Unlike previous workers, who had blamed vagus stimulation, he suggested that stimulation mediated by sympathetic nerves might be responsible. The weakness, giddiness, perspiration, and faintness are not unlike the effects produced by adrenaline and the rise in pulse rate and blood pressure which are observed in some cases might be produced in the same way. Indeed part of the rise in blood sugar level also could be attributed to release of adrenaline. Other workers have supported this view; for example, Smith and his colleagues (1953) who noted that the early post-prandial symptoms could be reproduced by injecting adrenaline, while Pulvertaft (1954) noted an increase in blood catechol levels, though they did not correlate well with the onset of symptoms.

Electrocardiograph studies give some limited support to this view. Many workers (Smith, 1951), Roberts, Randall, Farr, Kidwell, McNeer, and Pack (1954), Pulvertaft (1954), Peddie, Jordan, and De Bakey (1957), and Duthie (1959) have carried out such studies. They show that changes in the electrocardiograph tracing begin five to 15 minutes after a meal and attain a maximum at 20 to 30 minutes. There is an increase in heart rate, varying from a few beats to 50 a minute. There is lowering or flattening of the T wave and a U wave may make its appearance or become more pronounced if already present. The S-T segment may be elevated or depressed and there may be some peaking of the P wave.

Although these or similar features have been reported by all those who have studied the matter there is no agreement as to their significance. They have been attributed to potassium deficiency (Smith, 1951) and to coronary arterial insufficiency (Roberts *et al.*, 1954). Pulvertaft (1954) noted that they were related to the rate of absorption of sugar from the intestine. Duthie (1959), who has made a special study of the problem, has been unable to find a

correlation between these changes and the rise in blood pressure or the fall in plasma volume or the severity of symptoms.

Thus, there is little disposition to regard a sympathetic stimulation as the major cause of the post-prandial symptoms though it may well be a contributory factor. It is possible that the falling blood volume, acting through aortic pressoreceptors, stimulates the outpouring of adrenaline and this may perhaps be responsible for the tachycardia and the maintenance of blood pressure as well as some of the symptoms.

*Potassium Loss.*—The idea that the muscle weakness and drowsiness which occur as part of the early post-prandial syndrome might be due to a temporary deficiency of potassium was first suggested by Smith (1951). He studied six patients after standard meals and high-protein meals and also after they had been given hypertonic glucose solution. He noted that whereas in normal control patients the potassium level remained unaltered, in patients liable to post-prandial symptoms it regularly fell to the lower limit of normal. When potassium was given intravenously, although the other components of the syndrome were unaffected, the weakness and fatigue were controlled. He suggested that the fall in potassium might be due to the release of an adrenaline-like substance or to unduly rapid absorption of carbohydrate, leading to rapid deposition of glycogen with binding of potassium inside the glycogen-storing cells.

Certainly the symptoms are quite like those of potassium deficiency and moreover the electrocardiographic changes, as have already been discussed, might well be due to the same cause. The idea has been criticised for the reason that the fall in serum potassium is not pronounced and such fall as there is tends to become evident rather late after the meal, when the symptoms are beginning to abate. However, it must be acknowledged that the serum potassium is not a true index of the level of potassium within the cells.

*Fall of Plasma Volume.*—One of the most consistent and notable changes to be observed in the early post-prandial phase is a reduction in the volume of blood in circulation.

Roberts and his colleagues (1954) seem to have been the first to draw attention to this matter. They examined 10 cases after total gastrectomy and four after subtotal gastrectomy, using the Evans blue method, and noted a marked fall in plasma volume which developed within 10 minutes after a meal of 50% glucose and reached a maximum between 30 and 40 minutes. Similar changes have been observed by several subsequent workers (Amdrup and Jørgensen, 1957; Hinshaw, Joergenson, Davis, and Stafford, 1957; Peddie *et al.*, 1957; Everson and Abrams, 1958; Weidner, Scott, Bond, and Shull, 1959).

The fall in plasma volume, as estimated by this method, averages about 5 or 6% but in severe cases it may exceed 10% or even 15%. A similar fall has been observed after a meal of fructose or mannitol or a meal rich in proteins.

There is general agreement that the fall in plasma volume is due to osmotic withdrawal of fluid from the plasma into the jejunal lumen as a result of the hypertonic meal. This view receives confirmation from the observation by Amdrup and Jørgensen that the fall of volume is related to the amount of fluid seen in the lumen.

Like all the other post-gastrectomy developments we have reviewed the fall of plasma volume is observed in patients without symptoms as well as in those with symptoms. Some observers have found a correlation between the extent of plasma volume change and the symptoms. Thus Amdrup and Jørgensen found the fall almost directly related to the intensity of symptoms, and Le Quesne and his colleagues came to a similar conclusion. Other workers (Peddie *et al.*, 1957; Everson and Abrams, 1958) were unable to confirm this result.

Duthie (1960) has studied the question in my department, using radio-iodinated human serum albumin as the marker substance. He investigated 20 gastrectomy patients with post-prandial symptoms and 20 who were symptom free. The maximum fall in plasma volume averaged 8·3% in the former group and 7·0 in the latter; the difference was not statistically significant. Moreover, he found that severe degrees of fall in plasma volume (more than 10%) were but little more frequent in patients with symptoms than in the symptom free.

ADDITIONAL FEATURES.—The observations reported above make it clear that many gastrectomy patients present a complex vasomotor post-prandial disturbance of which the central feature is the fall of plasma volume due to osmotic fluid shift into the intestine. However, all the changes which have been observed occur not only in patients with post-prandial symptoms but also in those who are symptom free, and in the opinion of most observers they are just as marked in the latter group as in the former.

It is clear therefore that there must be some factor of individual susceptibility or some other unidentified factor which determines which patients will develop symptoms.

Le Quesne, Hobsley, and Hand (1960) have demonstrated the existence of an individual susceptibility to falling plasma volume by applying

pneumatic tourniquets to the thigh. When inflated to obstruct the venous return, they abstract 400-700 ml. of blood from the circulation in the course of 15 to 20 minutes, which is closely comparable to the plasma volume change after a meal. In patients liable to post-prandial symptoms this procedure led to faintness and drowsiness whereas in other patients it was tolerated without noticeable effect.

It is indeed true that the plasma volume loss is hardly sufficient to account for symptoms in robust subjects (the loss is no more than every blood donor tolerates willingly) and the possibility of some additional factor must be considered.

Hinshaw and his colleagues believe that the factor concerned is a failure of the homoeostatic response to diminished plasma volume. The normal response should be a peripheral vasoconstriction, and this, they find, occurs in gastrectomy patients who are without symptoms. In those liable to post-prandial symptoms, on the other hand, digital plethysmography shows that instead of vasoconstriction there is an increase in the peripheral blood flow, sometimes up to 12 times the normal.

Another possible factor is pooling of blood in stagnant backwaters of the circulation, most probably in the vascular jejunum and its mesentery and the portal area as a whole. The usual methods of estimating plasma volume will not show such stagnation, for they measure the concentration of dye (or radioactive iodine) bound to the albumin and, apart from the normal disappearance rate, this concentration is altered only by escape of the non-albuminous fluid from the circulation.

Duthie (1959) has sought to demonstrate blood stasis by a modification of the plasma volume estimation, in which Evans blue is given in intermittent doses, on the basis that later doses might not mix with blood in stagnant areas, and in two patients with severe dumping he produced some evidence of blood stasis by this means. A more refined technique is to estimate the plasma loss in the usual way and also the packed cell volume (P.C.V.) at intervals after a meal. The recorded P.C.V. is then compared with the figure calculated from the initial P.C.V. as it would be modified by the plasma loss. In such observations on 35 cases Duthie found a striking correlation between blood stasis and symptoms.

MEDICAL CARE OF PATIENTS WITH POST-PRANDIAL SYNDROME.—In view of what is known about the early post-prandial syndrome, rational treatment should be directed to correcting the precipitate emptying of the stomach and minimizing the effects of the fall in plasma volume. The treatment embraces advice on diet and medication, attention to the general health, and adjustment of the way of life. Spontaneous improvement takes place in most cases during the first year or so, and it is reasonable to suppose that medical care will assist this process.

Every gastrectomy patient should be given proper advice about his diet, for the conditions under which digestion proceeds are entirely different and a diet designed to mitigate the pain of ulcer may be entirely unsuited to the post-operative state. Sometimes indeed milk and milk products seem to precipitate the post-prandial symptoms.

After gastrectomy it is essential to reduce the bulk of the meal. Different patients vary, but each should find his own capacity and not exceed it. To do so it is often a good plan to eschew bulky soups and sweets, and be content with a single course. Bulky carbohydrates, such as potatoes, should be limited and cooked fats should be reduced, though butter may be well tolerated. Though small in bulk the choice of food can be fairly wide and the meals can be made very appetizing to patients inured to long years of an ulcer diet. Meat is usually well tolerated, all kinds of vegetables, salads, and fruits, and even pickles, sauces, and condiments.

Medication should be reduced to the minimum after gastrectomy. There is no need for alkalies, antacids, and adsorbents and they may be positively harmful.

In addition to this kind of regimen, attention must be paid to the general health. Patients with post-prandial symptoms are often anaemic and under weight, and while these are usually the results of the syndrome, if they can be corrected the symptoms may be improved. Anaemia may respond to iron but if it is severe a transfusion of blood is desirable. For weight loss an anabolic steroid preparation may be tried. It has been claimed that good results may sometimes be obtained from insulin in small doses, administered just before the main meal.

It would seem rational to slow down the bowel motility by the use of ganglion blocking agents, but such treatment has proved disappointing. Finally, as an auxiliary to medical treatment, patients who can do so should be advised to lie down for half an hour after meals. This may prevent the attacks and will certainly diminish their severity.

SURGICAL TREATMENT.—Many different operations have been advocated in the past, according to differing views on the aetiology of the syndrome. On the theory that an obstruction of the afferent loop was responsible it seemed rational to relieve this obstruction by making an anastomosis between the afferent and efferent loops. As has been the fate of so many suggested treatments for this obscure

disease, the early results seemed promising but continued experience has not substantiated them. In the same way the Roux-Y operation, while believed to be effective for bilious vomiting, gives no relief to the vasomotor features of the post-prandial syndrome. On the basis of present-day views on the aetiology the rational treatment would be to diminish precipitate emptying either by enlarging the capacity of the stomach or by reducing the size of the outlet.

Attempts have been made to enlarge the capacity by transplanting an isolated segment of colon so that it lies between the gastric remnant and the jejunum. Few surgeons have published their experience of this operation so that there is little reliable evidence about it. Probably it can be inferred that few surgeons have been sufficiently impressed by their experience to be encouraged to repeat it.

On the whole, better results seem to have been obtained from methods designed to diminish the rate of outflow tract from the stomach, and at the present time this type of operation is the procedure of choice for severe cases of the early post-prandial syndrome.

The most satisfactory method is to convert to the Billroth I gastroduodenal anastomosis, which not only reduces the size of the stoma and introduces the resistance of the relatively narrow duodenum, but also gives benefits related to the absorption of fat (see below). If conversion to Billroth I is technically too difficult (in my experience this is rare) the alternative is to dismantle the Polya stoma, and make a new anastomosis of smaller size.

The steps of the conversion to Billroth I are as follows:—

After full exploration to exclude other lesions, the first step is to free the region of the gastrojejunal anastomosis from all adhesions and, in the case of a retrocolic anastomosis, to free it from the mesocolon. Next, the stomach remnant must be mobilized freely to enable it to be brought across to the duodenum without tension. On the lesser curve, the stomach should be mobilized completely up to the oesophageal orifice. The greater curve should also be freed almost to the fundus, but at least one of the short gastric vessels must be retained to maintain the circulation. Great care should be taken to avoid damage to the spleen or its pedicle, which might prejudice this blood supply.

When this has been done, attention is directed to the duodenal stump. It is exposed by dividing the peritoneal adhesions over it and dissected free. The second and third parts of the duodenum, along with the pancreas, are also sponged forwards to ensure greater mobility. The duodenum is now opened either at its blind end or by a longitudinal incision extending to the second part.

At this stage attention is turned again to the gastrojejunal anastomosis. Sometimes it is satisfactory to undo the anastomosis and repair the defect in the jejunum with an infolding stitch. More often this would leave an irregular, dog-eared and narrowed jejunum and it is better to resect a few inches cleanly and restore continuity by end-to-end anastomosis.

The open end of the gastric remnant must then be reduced in size by a continuous suture starting from the lesser curvature, the aim being to make the opening in the stomach roughly commensurate with that previously made in the duodenal stump. Generally about 3 cm. suffices. Finally, this opening is united to the duodenum. All the suturing must of course be done with great care, and particularly so for the final stage, the gastro-duodenal anastomosis. The aim is to obtain exact apposition with neat stitching, to minimize the risk of oedema and obstruction of the stoma during the ensuing few days. If this is done, the post-operative course should be unremarkable.

### Bilious Vomiting

As has already been said, bilious vomiting may occur as part of the early post-prandial disturbance or as an isolated phenomenon. It varies also in severity. One patient may complain of little except that from time to time he feels a little nauseated, vomits a few mouthfuls of pure bile, and is then once more all right. Another patient has attacks of epigastric discomfort, building up for a few hours and culminating in the regurgitation of a large quantity of bilious fluid. In such cases there may be other post-prandial symptoms, much weight loss, and severe disability.

The cause of the bile vomiting is not fully understood. There is, of course, no difficulty in explaining why the vomit contains bile and not food, for the vomiting usually occurs an hour or so after a meal and by that time all food has left the stomach. Nor is it difficult to explain why so much bile, in such a pure state, should appear so long after a meal; presumably the cholecystokinin mechanism for emptying the gall bladder acts more slowly since food does not enter the duodenum. The real difficulty is to explain why, since the meal has passed normally towards the lower reaches of the bowel, there should be some impediment to the transmission of bile in the same direction.

The explanation generally favoured attributes this symptom to transient obstruction of the afferent loop, which gradually becomes distended with bile

and then suddenly releases it into the stomach. In some cases the cause of obstruction can be demonstrated at operation. This is particularly so where the gastrectomy has been of antecolic type with a large dependent afferent loop. In other cases no organic obstruction can be demonstrated at operation and it must be supposed that the obstruction is caused by kinking or rotation of the afferent loop when the stomach is distended with food. Various methods of operation have been devised for the treatment of bilious vomiting. They have been reviewed by Capper and Welbourn (1955). Where the vomiting is a relatively insignificant feature of a post-prandial syndrome in which the vasomotor symptoms predominate, it seems probable that the most satisfactory treatment, as already discussed, is to convert the anastomosis to one of Billroth I type. On the other hand, where the bilious vomiting is the principal cause of disablement, a more satisfactory method is to create a Roux-Y-shunt. The afferent loop is divided just short of the anastomosis. The end abutting on the anastomosis is closed. The proximal end is then inserted, end-to-side, into the efferent loop some 6 or 8 in. further distally. Conyers, Hall, Laing, Pulvertaft, and Willson-Pepper (1960) have recently reported their experience of 54 cases treated in this way, with 19 excellent results and only two which could be classified as unsatisfactory.

### The Late Hypoglycaemic Syndrome

As its name indicates, this syndrome occurs late after a meal (two to three hours) and coincides with the depression of the blood sugar level which occurs in some gastrectomy patients at that stage. Although hypoglycaemia is fairly common after gastrectomy the hypoglycaemic syndrome is generally regarded as rare. Perhaps this is because many patients learn to recognize the premonitory symptoms and prevent the attacks by taking food.

The attacks are similar to those of hypoglycaemia due to other causes and are characterized by tremor, giddiness and excitement, sweating and muscular weakness. In severe cases they culminate in unconsciousness.

Although the relation to hypoglycaemia seems to be established there are some puzzling features. It is not yet really certain why the hypoglycaemia occurs. The usual explanation, that it is due to a delayed and excessive output of insulin in response to the initial hyperglycaemia, does not accord with the observation that no similar output follows hyperglycaemia induced by intravenous glucose. According to Smith and his colleagues (1953) the essential abnormality lies in oversensitivity to insulin, which aggravates the hypoglycaemia and makes it unduly prolonged.

Patients who suffer from the hypoglycaemic syndrome do not necessarily give an abnormal response to a glucose tolerance test carried out during an interval between attacks. It looks as though some additional factor is necessary to provoke an attack. The essential diagnostic step is to examine the blood sugar during an attack, when it will certainly be below 50 mg.% and may be as low as 20 mg.%.

Dietetic treatment usually suffices to prevent attacks. The patient must be advised to avoid rapidly assimilable carbohydrates in order to prevent the extremes of blood sugar fluctuation caused by rapid absorption. However, despite this general recommendation the patient may carry sugar to use in emergencies when an attack seems imminent. In severe cases it may be necessary to advise conversion to a Billroth I anastomosis.

### The Malabsorption Syndrome

Under this generic title we include various disturbances after gastrectomy due to impaired absorption of foodstuffs, iron, and vitamins. They may occur as isolated phenomena but usually, especially when severe, they occur as concomitants of severe post-prandial syndromes.

Loss of Weight.—It is a common experience that the majority of patients after gastrectomy fail to maintain their "tabular" weight (the weight appropriate, according to accepted tables, for their height and age), and many fall far below that level. Anderson, Gunn, and Watt (1955), in a review of nearly 500 cases from my unit, found that 55% of the men and 65% of the women were more than 5% underweight. More recently Duthie (1960) in a smaller series of 89 cases found that an even higher proportion (67%) had lost some weight. He confirmed the general view that the weight loss tends to be greatest in patients with severe post-prandial symptoms.

Apart from extraneous causes, such as tuberculosis, the weight loss may be due to three causes, reduced intake, vomiting, and impaired absorption. Reduced intake is of especial importance in those patients who find they have to limit the bulk of their meals in order to prevent post-prandial disturbances. Sometimes also such patients are nauseated, and their appetite is affected in consequence. A particularly difficult problem is seen occasionally in elderly patients with persistent impairment of general health, who become depressed and apathetic and anorexic, and go downhill from simple starvation.

However, the great majority of gastrectomy patients have good appetites and for them the cause of the weight loss is to be found in some defect of absorption, particularly of fats. This is indeed obvious from the naked eye character of the stool, which may be bulky, pale, and greasy. It is readily confirmed by estimation of the total fat content.

There are several possible causes of the malabsorption.

(1) Mistiming of the bile and pancreatic secretion may be partly responsible, for normally bile and pancreatic juice are secreted in response to the presence of food in the duodenum and their secretion is slow to match the normal emptying of the stomach. After gastrectomy the secretory response is poor and sluggish, so emulsification and digestion are impaired.

(2) It has been suggested that the diminished gastric acidity after gastrectomy may lead to impaired pancreatic secretion and vagotomy also has been claimed to have a similar effect (Butler, 1960).

(3) The attention focused in recent years on idiopathic steatorrhoea has led to the suggestion that the steatorrhoea after gastrectomy might have a similar cause. Shiner and Doniach (1958) have examined portions of jejunal mucosa removed at biopsy from 11 gastrectomy cases. The appearance was entirely normal in nine cases, but in the remaining one there was marked atrophy of the villi with an increase in total thickness of the mucosa. Joske and Blackwell (1959) made similar findings in four patients who suffered from malabsorption after gastrectomy.

It seems doubtful, however, if jejunal biopsy material can give valid information in these cases, for we know from simple examination at operation that the efferent loop of jejunum, from which the biopsy tissue is removed, is far from representative of the small intestine as a whole.

(4) It seems probable that the main cause of the weight loss is the obvious one, namely that absorption of food products from the small intestine is impaired as a result of intestinal hurry. Radiological studies show that the barium commonly reaches the caecum within 15 minutes, and while the barium meal is doubtless a fallacious index of intestinal movement under normal conditions there can be no doubt, from a mass of clinical evidence, that the passage of ordinary food through the intestine may be very rapid.

Support for this view is given by observations on the absorption of radioactive fat. When fat tagged with radioactive iodine is given by mouth to patients after gastrectomy, the blood level during the first hour rises at the normal rate, but the total absorption, as measured from the amount of radioactive fat excreted in the stools, may be far below the normal.

The treatment should depend upon the severity of the weight loss. In minor degrees, that is to say less than 10 lb. below tabular weight, no treatment is necessary. Indeed the patient should be reassured and congratulated, for it makes for general fitness and also, as Walker, Watson, and Watt (1958) have shown, it may reduce the liability to coronary disease. In more severe degrees of weight loss, the first indication is to exclude extraneous causes, such as tuberculosis, malignant disease, intestinal fistula. A check should be made of the food intake. Postprandial disturbances causing anorexia or vomiting may require treatment. Insulin has been advised to improve the appetite and ensure utilization of the sugar spilled over during the hyperglycaemic phase. Anabolic steroids may be helpful in severe anorexia. Rarely a gluten sensitivity may be found responsible.

However, in most cases of severe weight loss if ordinary dietectic remedies are unavailing and if all other causes have been excluded the question of further operation should be considered. On the basis that intestinal hurry is the factor responsible the rational treatment is to convert to the Billroth I anastomosis, and this is in fact an effective method of relieving the weight loss.

ANAEMIA.—Hypochromic anaemia is common after gastrectomy. Anderson *et al.* (1955), using the Sahli method, found that over 40% of the women patients had haemoglobin levels below 20, while about 20% had a level below 70. The tendency to anaemia is much less in men.

In some such cases, continued blood loss is one of the factors involved. Most of Duthie's male patients with anaemia gave a history of bleeding haemorrhoids, and probably the special liability of women to anaemia is due in part to the menstrual loss. The possibility of persistent occult bleeding from erosions in the vicinity of the anastomosis must be considered (Witts, 1956). However, this is clearly not the only factor, and in the majority of cases there is also some defect in the intake of iron due, for example, to anorexia, unsuitable diet, vomiting, or in its absorption Smith (1956).

As in so many other aspects of the post-gastrectomy syndromes, the question at issue raises problems concerned with physiology and once again it focuses attention on the gaps in our knowledge of the normal process. It is generally agreed, based on animal experimentation, that the main site for absorption of iron is in the duodenum and upper jejunum, so it might be supposed that the anaemia after gastrectomy might be due to the short circuiting of this segment by the gastrojejunal anastomosis.

However, Duthie (1959) has shown, by studies on two patients converted from the Polya to the Billroth, and two patients converted from Billroth to Polya, that the absorption of iron is in no way different in the two types of anastomosis.

The reduced gastric acidity after either form of gastrectomy may well be a factor leading to impaired iron absorption, but it seems likely that the main factor is the same as is responsible for the weight loss, namely, intestinal hurry. This is confirmed by the common finding that the absorption of inorganic iron is not impaired and may even be enhanced, provided it is given in small doses at frequent intervals. Further confirmation is given by the observation of Baird, Blackburn, and Wilson (1959) who showed that the absorption is reduced if the iron is given with a full meal, when intestinal hurry may be presumed to be the factor responsible. In the treatment it is necessary to remember that anaemia is easier to prevent than cure. It is important to give the patient a good start, so the haemoglobin level should be checked before he leaves hospital and if there is a serious deficiency blood transfusion should be performed.

Iron should be given with caution, for excessive doses readily cause diarrhoea. The best method, therefore, is to give small doses over long periods. On his return home after gastrectomy the patient should take iron continuously for a few months. Thereafter the haemoglobin level should be checked from time to time. Since many patients without other symptoms are apt to disregard the minor effects of anaemia it is a good plan to recommend that in any case at each anniversary of the operation iron medication should be given for a month or so. Where anaemia develops despite these precautions a search should be made for sources of hidden blood loss, and the appropriate treatment carried out.

Macrocytic anaemia is well recognized as a late sequel to total gastrectomy and in recent years a few cases have been reported after partial gastrectomy (Blake and Rechnitzer, 1953; Girdwood, 1956). The anaemia is due to faulty absorption of vitamin $B_{12}$ and makes its appearance only after an interval of several years, owing to the presence in the liver of large stores of the vitamin. Girdwood (1960) has shown that the absorption of folic acid is normal. In the treatment, administration of vitamin $B_{12}$ is quickly effective.

MALABSORPTION OF VITAMINS.—Apart from $B_{12}$, occasional cases have been reported of late symptoms due to failure in the absorption of other members of the vitamin B complex. They are so rare that the possibility of additional causes must be suspected, for example, a dietetic deficiency or a gastro-colic fistula or an intestinal cul-de-sac. Where there is no such cause, the symptoms yield rapidly to administration of the vitamin complex.

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# THE USE OF CHOLECYSTOKININ TO TEST GALL BLADDER FUNCTION IN MAN

BY

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In 100 subjects the cholecystokinin test has been used in conjunction with the secretin test of gall bladder function. The response of the normal gall bladder to a standard dose of pancreozymin has been studied and the results in patients following cholecystectomy and in the presence of biliary tract disease have been recorded and contrasted with the results obtained by the secretin test and oral cholecystography. These are sufficiently characteristic to warrant the conclusion that used in this way the cholecystokinin test provides a new and valuable semi-quantitative estimate of gall bladder function.

Radiographic visualization of the biliary tract is now so excellent technically that tests of gall bladder function based on duodenal drainage, never popular in Britain, have been largely discarded. Although cholecystography and cholangiography may demonstrate the presence of non-opaque stones in the biliary tract there is still need of an alternative method of investigation, especially in those instances where radiography is less helpful, as when the gall bladder does not outline with dye, in more deeply jaundiced patients, or after cholecystectomy.

Among other methods of investigating gall bladder function in man are the Meltzer-Lyon, secretin, and sodium dehydrocholate tests.

## The Meltzer-Lyon Test

Meltzer (1917) in a footnote to a paper devoted to a discussion of the concept of "contrary innervation" in relation to gall bladder emptying suggested that a 25% solution of magnesium sulphate applied topically to the duodenal mucosa through a duodenal tube would relax the sphincter at the duodenal papilla and the gall bladder would contract. Lyon (1919, 1923) acted on this suggestion, and, using both magnesium sulphate and olive oil, applied the method first to diagnose and later to treat biliary tract disease. Though failure to obtain concentrated bile ("B" bile from the gall bladder) after several attempts was taken in the absence of liver dysfunction to indicate biliary disease, greater significance was laid on the presence of abnormal numbers of cells and crystals in the specimens of bile. Juniper and Burston (1957) have recently reviewed the merits and limitations of this aspect of the Meltzer-Lyon test.

## The Secretin Test

The preparation of secretin extracts sufficiently pure to permit their use in man led to a further method of studying gall bladder function. Extracts of secretin have proved to be choleretic agents in man as in animals, increasing the flow of bile from the liver (Grossman, Janowitz, Ralston, and Kim, 1949). When Ågren and Lagerlöf (1936) and Ågren, Lagerlöf, and Berglund (1936) undertook quantitative recovery of the duodenal contents uncontaminated by gastric juice and made a quantitative assay of pancreatic function after the intravenous injection of secretin, they soon appreciated that the content of bile pigment in the fractions of duodenal contents following secretin might afford an index of gall bladder function. It is possible to distinguish three main types of response (Ågren and Lagerlöf, 1937).

Type I: Normal Gall Bladder.—In normal subjects the sphincter of Oddi is competent and closes following the injection of secretin. The normal gall bladder distends as it receives hepatic bile. After an initial flow of bile the bilirubin concentration of the second or third 10-minute sample of duodenal contents falls to a very low level, frequently to zero. Thirty or 40 minutes after the injection of secretin the sphincter relaxes, and this is accompanied by a rise in the bilirubin concentration in the later samples. Two modifications of this "classical normal response" may be produced by a spontaneous

contraction of the gall bladder during or just before the test. In the first variant spontaneous contraction of the gall bladder in the early stages of the test leads to high values of bilirubin in the duodenal contents which may persist in several fractions after the giving of secretin (Ågren and Lagerlof, 1937). A rising curve may result (Dreiling and Lipsay, 1951). In the second variant, if the gall bladder has emptied before the test, it may accept most of the bile produced by the liver in response to secretin. The concentration of bilirubin remains low or absent throughout the test.

TYPE II: NON-FUNCTIONING GALL BLADDER OR POST-CHOLECYSTECTOMY.—In these circumstances the sphincter of Oddi is incontinent and throughout the test period bile flows continuously into the duodenum. During the height of pancreatic secretion the concentration of bile is lowered by dilution with pancreatic juice, but not to the extent seen in Type I. A second characteristic of this group is the increased volume of duodenal contents following stimulation by secretin (Ågren and Lagerlöf, 1937). This is due to the diluent action of the hepatic bile and may be associated with lowered concentrations of bicarbonate in the duodenal samples (Burton, Evans, Harper, Howat, Oleesky, Scott, and Varley, 1960).

TYPE III: COMPLETE BILIARY OBSTRUCTION.—Bile pigment is absent or practically absent throughout the test. The second variant of the normal response can be distinguished from this response by giving magnesium sulphate before ending the intubation to induce a flow of "B" bile from the gall bladder (Dreiling and Lipsay, 1951).

The existence of these three main types of response has been confirmed by other workers (Diamond, Siegel, and Myerson, 1940; Pratt, Brugsch, and Rostler, 1940; Pollard, Miller, and Brewer, 1942; Lake, 1947; Snape, Friedman, and Swenson, 1948). Ågren and Lagerlöf (1937) describe transitional and overlapping types. Of these, Dreiling and Hollander (1948) and Dreiling (1950) consider that a response (called by them the "AP response") occurs sufficiently often in post-cholecystectomy cases to justify its being regarded as a separate group. It is a variant of type II, intermediate between type II and type I, observed in association with incomplete organic obstruction of the common bile duct due to stone, stenosis, or post-operative stricture in certain subjects in whom the bile ducts are said to dilate and take on the function of a bile reservoir.

The biliary pigment response in the secretin test has been correlated with the clinical findings and oral cholecystography by Snape *et al.* (1948) and by Dreiling and Lipsay (1951). Close agreement is the rule except when the liver is damaged or when low volumes (less than 50 ml./80 minutes) are recovered from the duodenum in severe pancreatic insufficiency. Dreiling and Lipsay concluded that the secretin test is especially valuable in those instances where information cannot be obtained from cholecystography, when intestinal absorption is poor, when the gall bladder has been removed, or in jaundiced patients. The subsequent introduction of biligrafin for intravenous cholangiography and cholecystography has of course overcome difficulties due to poor absorption of the dye.

### THE SODIUM DEHYDROCHOLATE TEST

Lans, Stein, and Meyer (1951) have given this hydrocholeretic agent intravenously and found that the amount of bile pigment in duodenal samples is greater in patients with biliary disease than in normal subjects. It is claimed that the test is more sensitive than the secretin test but Lipsay (1951) after a trial concluded that "decholin" possessed no advantage over secretin as a biliary stimulant.

A second hormone, distinct from secretin, was isolated from extracts of duodenal mucosa by Harper and Raper in 1943. Whereas secretin produces a large volume of alkaline pancreatic juice with a low enzyme content, pancreozymin increases the enzyme output selectively. In 1949, Crick,

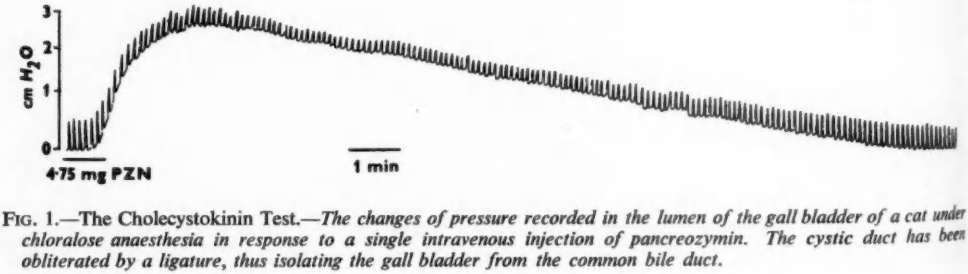



FIG. 1.—The Cholecystokinin Test.—*The changes of pressure recorded in the lumen of the gall bladder of a cat under chloralose anaesthesia in response to a single intravenous injection of pancreozymin. The cystic duct has been obliterated by a ligature, thus isolating the gall bladder from the common bile duct.*

Harper, and Raper produced a preparation of pancreozymin sufficiently pure to use in man. Duncan, Harper, Howat, Oleesky, and Varley (1950) confirmed that pancreozymin, in man as in animals, seems to act as a specific enzyme stimulant.

While investigating the effects of these duodenal hormones, secretin and pancreozymin, on the external secretion of the pancreas in man, we have also recorded the effects of preparations of pancreozymin on the gall bladder. Following the intravenous injection of pancreozymin extracts in anaesthetized cats there is not only an increased output of pancreatic enzymes but also a contraction of the gall bladder (Fig. 1). This latter action of these extracts we attribute to the presence in them of cholecystokinin. Since one of the tests of pancreatic function in man with which we have been concerned involves the quantitative recovery of duodenal contents after the intravenous injection of secretin followed 30 minutes later by pancreozymin, we have obtained data which afford the basis for a new semi-quantitative test of gall bladder function, a preliminary report of which has already been given (Duncan *et al.*, 1952). The present paper records our further experience of this test and its use in the diagnosis of biliary tract disease.

Ivy, Drewyer, and Orndoff (1930) were unable to proceed with the use of their preparations of cholecystokinin in man, either for therapeutic or diagnostic purposes, because they led to allergic reactions. The only other records of cholecystokinin having been given to man, which we have been able to trace so far, have been its exploratory use by Denton, Gershbein, and Ivy (1950) and the clinical trials by the Stockholm group (Jönsson and Brodén, 1955; Brodén, 1956, 1958; Adlercreutz, Jorpes, Mutt, and Wegelius, 1957; Edholm, 1958; and Jorpes, Mutt, Tomenius, and Backlund, 1958). These workers gave cholecystokinin after oral cholecystography in order to study emptying of the gall bladder and in some cases succeeded in demonstrating the outline of the cystic and common bile ducts. Marks (1959) has recently described the variation of icteric index in the duodenal aspirate from seven normal subjects and 19 patients to whom pancreozymin had been given.

## Methods

Secretin and pancreozymin are prepared from pig intestine and assayed against standard preparations according to the methods of Crick *et al.* (1949). Preliminary tests of toxicity in mice and for anaphylaxis in guinea-pigs are carried out. The final products are freeze-dried powders soluble in water. Stored in the dark at 4°C. no appreciable loss of potency occurs in either extract kept for over two years. Immediately before use the appropriate amount of extract is dissolved in pyrogen-free distilled water and given intravenously. The usual dose of both secretin and pancreozymin has been 1·7 units per kilogram of body weight, the secretin being dissolved in 10 ml. and the pancreozymin in from 16 to 20 ml. of sterile distilled water. When given slowly into a vein in these dilutions no reactions have been observed after secretin injections and only rarely have reactions followed the administration of pancreozymin (Burton *et al.*, 1960).

Though we have in a number of cases demonstrated the effects of cholecystokinin radiographically, our usual practice has been to intubate the duodenum and give secretin followed by pancreozymin 30 minutes later. In this way not only can a simultaneous estimate be made of pancreatic and gall bladder function, but the cholecystokinin test can be compared and contrasted with the secretin test of gall bladder function. An additional advantage of this technique is the ease with which duodenal juice can be accurately and quantitatively collected when a brisk flow of juice is initiated and maintained throughout the test by giving secretin.

The subject fasts for 12 hours before the test. A double lumen radio-opaque tube weighted by a thin rubber bag containing 1·5 ml. of mercury is passed and so sited that one passage drains the stomach and the other the duodenum. To ensure this the position of the tube is adjusted by radioscopy immediately before the test period. With the patient reclining on a couch, aspiration of both tubes is maintained at a continuous negative pressure of not more than 40 mm.Hg. Salivary ejectors are used throughout the test. By these means duodenal juice uncontaminated by gastric contents is quantitatively recovered and collected in successive 10-minute fractions.

After at least two control periods of 10 minutes each (specimens C1 and C2) secretin is given. The duodenal juice obtained in response to the secretin is collected in three 10-minute fractions (specimens D1, D2, and D3). Some 25 to 30 minutes after the injection of secretin, pancreozymin is given and the collection is continued for a further 30 minutes (specimens D4, D5, D6). The volume of each fraction of duodenal juice is estimated and the bilirubin index is measured by Meulengracht's method. The "output of bilirubin units" is obtained by multiplying the bilirubin index by the volume of the sample in millimetres.

In comparing the mean results in normal subjects with those in post-cholecystectomy cases and in patients suffering from gall bladder disease, the t test has been applied, using the normal series only for the estimation of variance (Pearson and Hartley, 1954).

## Results

Physiological Effects of Extracts of Pancreozymin on Gall Bladder of Man.—In a normal subject when secretin (1·7 units per kilogram of body weight) is given intravenously, the shadow of the gall bladder outlined by cholecystography enlarges progressively during the next 30 minutes.

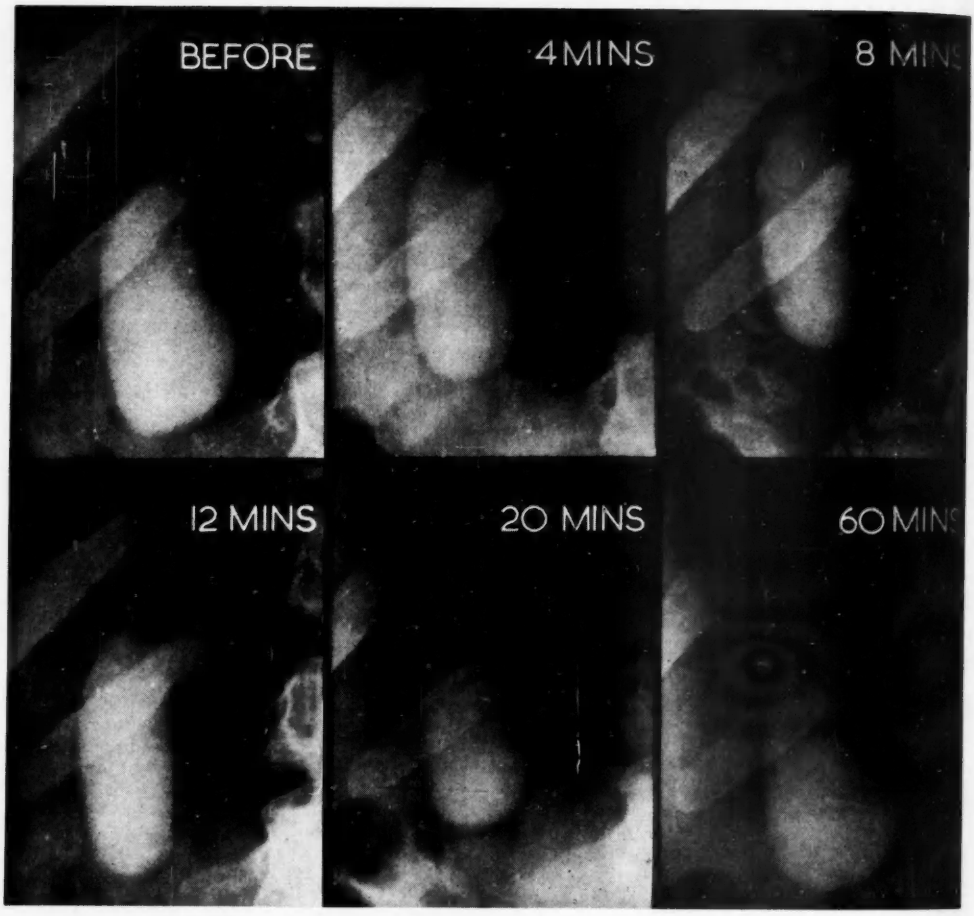



FIG. 2.—The Cholecystokinin Test.—*Serial cholecystograms taken before and at intervals after an injection of 1·7 units/kg. body weight of pancreozymin in man.*

After the injection of pancreozymin (1·7-2·25 units per kilogram of body weight) the gall bladder is reduced in size, most markedly at about the twelfth minute (Fig. 2). By Siffert's technique (1949) of computing gall bladder volume it has been shown that this dose of pancreozymin reduced the gall bladder by some 40 to 50% of its resting volume (Fig. 3). When pancreozymin is given without a preceding injection of secretin the volume of duodenal contents aspirated within 10 minutes is 24 ml., a figure which corresponds with the degree of contraction observed on radiography. Over 30 minutes the observed volume is 38 ml., but part of this is hepatic bile together with small amounts of intestinal and pancreatic secretion (Fig. 4).

SECRETIN-CHOLECYSTOKININ TEST OF GALL BLADDER FUNCTION IN NORMALS.— A typical example of the volume and bilirubin index of the duodenal juice obtained in response to secretin followed in 30 minutes by pancreozymin is shown in Fig. 5a. In response to secretin a rapid flow of juice is established which is greatest in the first 10-minute period and gradually diminishes. When pancreozymin is given a second increase in volume results which is largely due to the cholecystokinetic effect of the extract

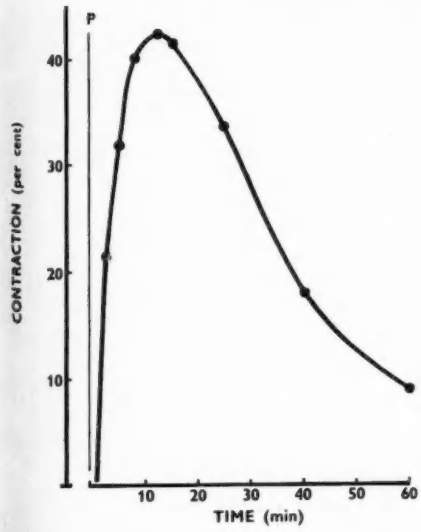



FIG. 3.—The Cholecystokinin Test.—*The change in volume of the human gall bladder in response to 1·7 units/kg. of body weight of pancreozymin, computed from serial cholecystograms by the method of Siffert (1949). The resting volume of the gall bladder was 46·3 ml.*

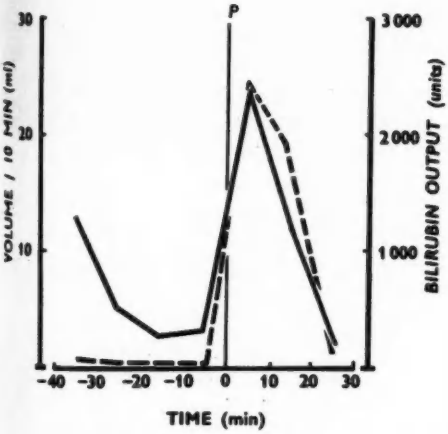


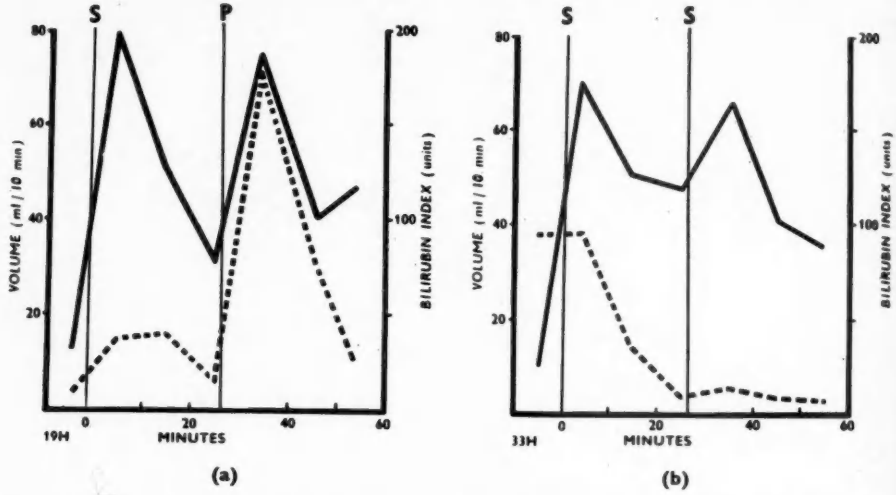

FIG. 4.—The Cholecystokinin Test.—*Volume of duodenal contents and output of bilirubin units obtained in response to 1·7 units/kg. of body weight of pancreozymin (P) alone.*

———— *Volume* - - - - - - - - *Bilirubin*

since the fluid collected becomes heavily stained with gall bladder bile. The bilirubin index increases greatly in the sample collected 10 minutes after the pancreozymin injection and then falls over the next 20 minutes. The effect of pancreozymin preparations on gall bladder contraction becomes even more striking when the diluent effect of pancreatic and intestinal juice is obviated by expressing the results as total output of bilirubin units (Fig. 5c). Should a second injection of secretin be given in place of pancreozymin the rise in volume which results is not accompanied by a rise in the bilirubin index comparable to that following pancreozymin, since in this case the increased flow of juice is due to further secretin stimulation of the pancreas and a slight choleretic effect on the liver (Figs. 5b and d).

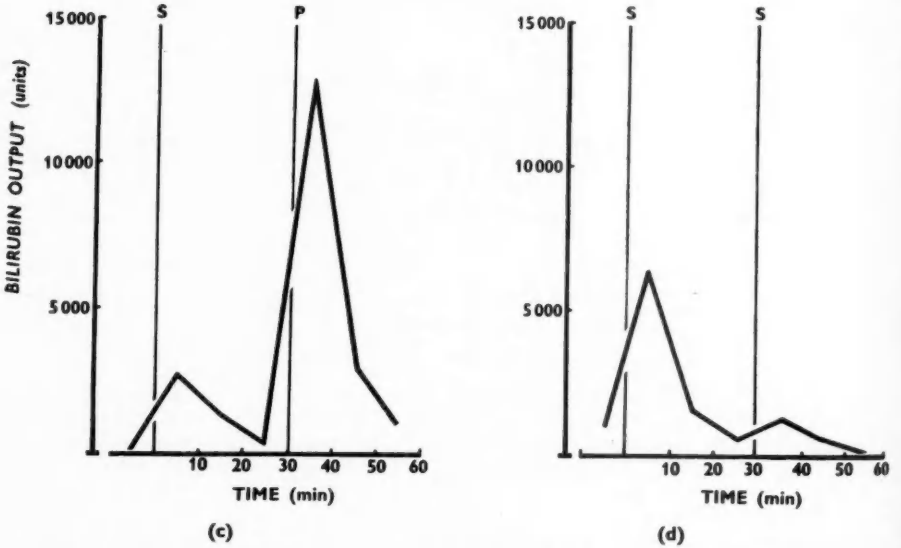
The normal group comprises 32 individuals: (*a*) 18 healthy medical students aged 21 to 27 years in whom the gall bladder was assumed to be normal; (*b*) seven adult patients varying in age from 35 to 64 in whom the gall bladder was shown to be normal radiologically, or at operation, or necropsy; and (*c*) seven adult patients, aged 27 to 64, who had previously suffered from pancreatitis but in whom the gall bladder was proved to be normal.

The mean results of the bilirubin index and output of bilirubin units in each 10-minute sample of this normal group are shown in Fig. 6 and Table I. So far as can be judged from the responses for 30 minutes after secretin, 20 of the 29 subjects in whom complete data are available showed a classical type I response of Ågren and Lagerlöf (1937). The mean minimum concentration in any of the three 10-minute samples obtained in response to secretin was $3 \pm 0{\cdot}6$ units ($\sigma = 2{\cdot}7$) in these 20 normal subjects. A minimum value of less than 10 units (mean $+ 2{\cdot}58\sigma$) has been accepted as normal for this type I response over 30 minutes. Dreiling and Lipsay (1951), who observed the biliary response to secretin for 80 minutes, considered a dilution of 5 units or less in any one specimen to be normal, above 10 units to be abnormal, and between 5 and 10 units to be equivocal. Of the remaining nine cases, six showed the first and three the second variant of the normal response. In all 29 subjects a well-marked cholecystokinetic effect was observed. The mean maximal bilirubin index after pancreozymin was $262 \pm 34$ units (range 82-900; $\sigma = 182$). In only one individual was the maximum index after pancreozymin less than 100 units. The mean total output of bilirubin units in the 20 minutes after pancreozymin in specimens D4 and D5 collected during the period when the gall bladder was contracting was 16,093 $\pm$ 2,011 units (range 5,800-53,880). Expressed in terms of output per kg. of




FIGS. 5a and b.—The Cholecystokinin Test.—*Volume of duodenal contents and concentration of bilirubin in two normal subjects in response* (a) *to secretin* (*S*) *followed by pancreozymin* (*P*), *and* (b) *to secretin* (*S*) *followed by a second equal injection of secretin* (*S*).

———— *Volume* – – – – – – – – *Bilirubin*




FIGS. 5c and d.—The Cholecystokinin Test.—*Output of bilirubin units* (*volume* × *bilirubin concentration*) *in response* (c) *to secretin* (*S*) *followed by pancreozymin* (*P*) *and* (d) *to secretin* (*S*) *followed by a second equal injection of secretin* (*S*) *in the same two normal subjects as Figs. 5a and b.*

TABLE I

RESULTS OF BILIRUBIN INDEX AND OUTPUT OF BILIRUBIN

| Groups and No. of Cases | Bilirubin Concentration: Samples C2 | Secretin D1 | Secretin D2 | Secretin D3 | Pancreozymin D4 | Pancreozymin D5 | Pancreozymin D6 | Maximum Post-pancreozymin Mean | Maximum Post-pancreozymin Significance | Output of Bilirubin Units: Samples C2 | Secretin D1 | Secretin D2 | Secretin D3 | Pancreozymin D4 | Pancreozymin D5 | Pancreozymin D6 | D4 + 5* Mean | D4 + 5* Significance | D4 + 5 (units/kg.*) Mean | D4 + 5 (units/kg.*) Significance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Normal* (29) | | | | | | | | | | | | | | | | | | | | |
| Mean | 13 | 49 | 18 | 10 | 255 | 62 | 10 | 262 | | 121 | 2,731 | 731 | 351 | 13,865 | 1,772 | 318 | 16,093 | | 257 | |
| S.E. | 3·9 | 8·3 | 4·4 | 3·0 | 35 | 9·6 | 1·8 | 34 | | 34 | 509 | 206 | 104 | 2,189 | 269 | 83 | 2,011 | | 29·6 | |
| *Cholecystectomy* (14) | | | | | | | | | | | | | | | | | | | | |
| Mean | 84 | 46 | 42 | 44 | 38 | 31 | 34 | 43 | $t=3{\cdot}70$ | 474 | 2,279 | 1,500 | 1,395 | 1,517 | 704 | 819 | 2,240 | $t=3{\cdot}86$ | 36 | $t=4{\cdot}19$ |
| Range | 4– | 4– | 1– | 1– | 1– | 1– | 8– | 10– | $P<0{\cdot}001$ | 132– | 400– | 20– | 10– | 20– | 7– | 24– | 352 | $P<0{\cdot}001$ | 1– | $P<0{\cdot}001$ |
| | 270 | 120 | 112 | 106 | 90 | 70 | 80 | 90 | | 816 | 8,320 | 4,180 | 3,480 | 5,320 | 2,240 | 1,860 | 6,120 | | 86 | |
| *Gall bladder disease* (27) | | | | | | | | | | | | | | | | | | | | |
| Mean | 62 | 65 | 35 | 22 | 45 | 33 | 22 | 48 | $t=4{\cdot}40$ | 440 | 4,118 | 1,352 | 727 | 2,587 | 918 | 559 | 3,505 | $t=4{\cdot}27$ | 52 | $t=4{\cdot}73$ |
| Range | 0– | 0– | 0– | 0– | 0– | 0– | 0– | 0– | $P<0{\cdot}001$ | 0– | 0– | 0– | 0– | 0– | 0– | 0– | 0– | $P<0{\cdot}001$ | 0– | $P<0{\cdot}001$ |
| | 240 | 240 | 176 | 108 | 154 | 104 | 78 | 154 | | 1,680 | 19,900 | 8,400 | 3,890 | 14,220 | 3,940 | 2,030 | 16,530 | | 178 | |
| *Non-vizualization* (20) | | | | | | | | | | | | | | | | | | | | |
| Mean | 64 | 62 | 32 | 25 | 39 | 30 | 23 | 43 | | 496 | 3,945 | 1,166 | 811 | 2,393 | 907 | 609 | 3,300 | | 47 | |
| Range | 0– | 0– | 0– | 0– | 0– | 0– | 0– | 0– | | 0– | 0– | 0– | 0– | 0– | 0– | 0– | 0– | | 0– | |
| | 240 | 162 | 88 | 108 | 154 | 104 | 78 | 154 | | 1,680 | 19,900 | 3,180 | 3,890 | 14,220 | 3,940 | 2,030 | 16,530 | | 178 | |
| *Poor vizualization* (4) | | | | | | | | | | | | | | | | | | | | |
| Mean | 57 | 62 | 23 | 18 | 62 | 39 | 16 | 65 | | 282 | 3,232 | 947 | 532 | 2,664 | 416 | 77 | 3,080 | | 55 | |
| Range | 18– | 15– | 8– | 2– | 18– | 18– | 14– | 18– | | 54– | 485– | 240– | 100– | 117– | 126– | 0– | 243– | | 4– | |
| | 102 | 136 | 56 | 40 | 90 | 90 | 18 | 90 | | 510 | 6,800 | 2,240 | 1,400 | 6,300 | 600 | 180 | 6,900 | | 126 | |
| *Adequate vizualization* (3) | | | | | | | | | | | | | | | | | | | | |
| Mean | 53 | 90 | 68 | 12 | 61 | 41 | 23 | 61 | | 230 | 6,455 | 3,134 | 426 | 3,780 | 1,663 | 873 | 5,443 | | 84 | |
| Range | 10– | 14– | 10– | 6– | 40– | 30– | 16– | 40– | | 90– | 184– | 320– | 168– | 1,680– | 1,050– | 368– | 2,760 | | 53– | |
| | 120 | 240 | 176 | 20 | 102 | 54 | 36 | 102 | | 360 | 18,700 | 8,400 | 860 | 7,600 | 2,860 | 1,800 | 10,460 | | 139 | |

* Data from 30 cases.

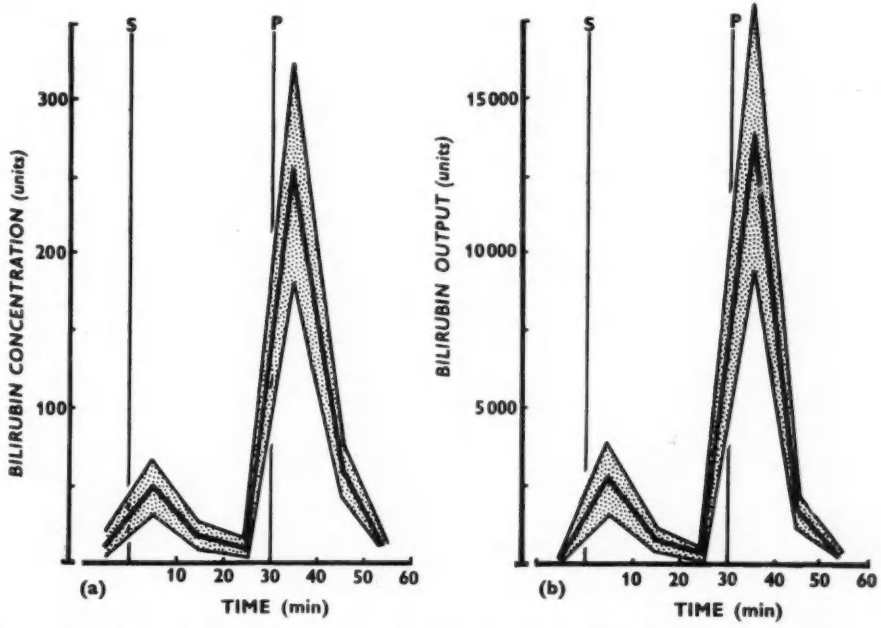



FIG. 6.—The Cholecystokinin Test.—(a) *Mean bilirubin concentration and* (b) *mean output of bilirubin units ±2 S.E. of the means in response to secretin and pancreozymin in 29 normal subjects.*

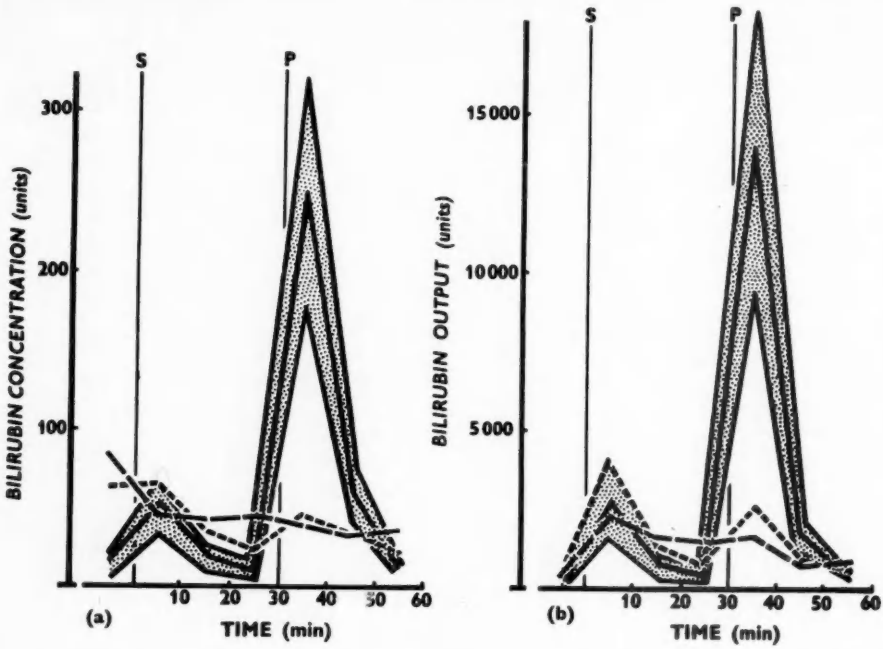



FIG. 7.—The Cholecystokinin Test.—(a) *Mean bilirubin concentration and* (b) *mean output of bilirubin units following cholecystectomy and in non-malignant gall bladder disease contrasted with the mean ±2 S.E. of mean of the normal group.*

——— *Normal (29 subjects)* — — — *Post-cholecystectomy* (14) - - - - - *Gall bladder disease* (27)

body weight the mean for this period was 257 ±29·6 bilirubin units (range 96-769).

SECRETIN-CHOLECYSTOKININ TEST AFTER CHOLECYSTECTOMY.—Observations were made on 14 patients (Fig. 8). The flow of liver bile elicited by secretin continued throughout the test, but at the peak of pancreatic flow samples became considerably diluted though not to a concentration as low as 10 units (Type II response of Ågren and Lagerlöf, 1937). This typical response to gall bladder ablation was observed in 12 of the 14 patients whose gall bladder had been removed; in none of these patients did the bilirubin index rise to any extent in response to pancreozymin. The mean results in this group are shown in Fig. 7 and Table I.

In two patients whose gall bladders had been removed the bilirubin index fell below 10 units. In both the duodenal contents were seen to be colourless during the aspiration of specimen D3. This corresponds to the "AP response" which Dreiling and Lipsay (1951) considered to be associated with partial obstruction of the common duct. This explanation was adequate in one of these patients who had benign strictures of both the right hepatic and common bile ducts, though not in the other who had mild chronic relapsing pancreatitis. In the former case the bilirubin response to pancreozymin remained at a low level; in the latter the response rose from less than one unit before to 82 units after pancreozymin. This was the only instance in which the physiological response of the choledochal sphincter to both secretin and pancreozymin was observed after cholecystectomy.

In three other subjects in this group the concentration of bile in post-pancreozymin samples was high, but since all three showed high bilirubin values following secretin and no further rise after pancreozymin to suggest a cholecystokinetic effect, there is no difficulty in distinguishing them from the normal group. Some biliary obstruction was suspected in these cases though the low output of pancreatic juice associated with chronic pancreatitis in two of them prevented to some extent dilution of the bile

samples. The suspicion was confirmed at operation in two of them, the obstruction being due in one to a gall stone proximal to a common bile duct stricture and in the other to stenosis of the common duct. It was not confirmed in the third.

On two occasions, both associated with bile duct obstruction, sudden and irregular fluctuations in bile staining were observed. This finding, which cannot be expressed quantitatively, may be more frequent than is recorded here. A tentative explanation is that it is associated with intermittent or ball valve obstruction of the bile ducts.

The mean maximal bilirubin index in the two 10-minute periods after pancreozymin in the post-cholecystectomy group was 43 units (range 10-90). The mean total output of bilirubin units in D4 and D5 was 2,240 units (range 35-6,120) or 36 units per kilogram of body weight (range 1-86). The differences between these means and the corresponding figures in the normal group are statistically very highly significant. In individual cases the units per kilogram of body weight may best reflect the absence of the gall bladder, since in no instance in the post-cholecystectomy group did the output for the 20 minutes following cholecystokinin exceed the lowest output (96 units per kg.) observed in a normal subject.

SECRETIN-CHOLECYSTOKININ TEST IN GALL BLADDER DISEASE.—The test was carried out in 27 patients (Fig. 8). The mean results are shown in Fig. 7 and Table I.

In the group with non-malignant disease of the biliary tract there are great differences in the capacity of the gall bladder to accept, concentrate, and void bile. At one end of the scale are patients in whom gall bladder function is completely destroyed and whose response to cholecystokinin is similar to that found after cholecystectomy: at the other are patients with stones in the gall bladder which nevertheless retains normal function. Between these two extremes varying degrees of functional impairment of the gall bladder are met. Twenty-seven patients in this group have been divided into three classes of functional derangement, based on the results of an oral cholecystography test.

The extent to which the results of the secretin test (over a 30-minute period) and the cholecystokinin test are in accord with this classification are set out in Table II. If a minimum post-secretin concentration of bilirubin in excess of 10 units is accepted as abnormal, the secretin test was abnormal in 15 of the 24 patients with known gall bladder and biliary tract disease. In 28 of the 29 normal individuals the maximum concentration of bilirubin after cholecystokinin exceeded 100, and in 12 of the 14 post-cholecystectomy cases the maximum bilirubin concentration did not exceed 80 units. On this basis we have separated the responses following cholecystokinin in cases of gall bladder disease into three groups: an abnormal group in which the maximal bilirubin concentration was less than 80; a doubtfully abnormal group with concentrations between 80 and 100; and the normal group with concentrations above 100. The cholecystokinin test was abnormal in 21 patients, doubtfully abnormal in two others, and normal in four. Of the four normal cholecystokinin tests, one showed agreement and one disagreement with the secretin test. The secretin test in the third is difficult to interpret but may represent the first variant of the normal response. In the fourth high bilirubin concentrations were present throughout the test (as in three patients of the post-cholecystectomy group) and no cholecystokinetic response was obtained. This patient had suffered from acute pancreatitis three months previously, and gall stones were found at subsequent operation in both gall bladder and common bile duct. The two doubtful responses were found in the poorly vizualized group. The secretin test was

TABLE II

COMPARISON OF ORAL CHOLECYSTOGRAPHY, 30-MINUTE SECRETIN, AND CHOLECYSTOKININ TESTS IN GALL BLADDER DISEASE

| Cholecystography | Secretin Test | | | | Cholecystokinin Test | | |
|---|---|---|---|---|---|---|---|
| | Normal | | Abnormal | | Normal | Doubtful | Abnormal |
| | Type I | First Variant of Normal | Type II | Type III (or Second Variant of Normal) | (Bilirubin index > 100) | (80—100) | (<80) |
| Non-vizualization—20 patients | 5 | 1 | 12 | 2 | 3 | 0 | 17 |
| Poor vizualization—4 patients | 2 | 0 | 2 | 0 | 0 | 2 | 2 |
| Adequate vizualization—3 patients | 2 | 0 | 1 | 0 | 1 | 0 | 2 |
| Total (27 patients) | 9 | 1 | 15 | 2 | 4 | 2 | 21 |
| | 10 normal | | 17 abnormal | | | | |

normal in one of these and doubtfully abnormal in the other.

In two jaundiced patients no bile was recovered after secretin though pancreatic function was adequate. The presence of clinical jaundice and the absence of bile in the cholecystokinin test distinguished this response from the second variant of the normal type I secretin response. In both patients at later operation a solitary stone was found blocking the common bile duct.

The mean maximal bilirubin index in the two 10-minute periods after pancreozymin in this group with biliary tract disease was 48 units (range 0-154 units). The mean total output of bilirubin units in the 20 minutes following pancreozymin (specimens D4 and 5) was 3,505 units (range 0-16,530 units) or 52 units per kilogram of body weight (range 0-178 units). On statistical comparison with the normal group the reduction in all three means was found to be very highly significant. The minimum output of bilirubin units per kg./20 min. for the normal group, 96 units per kg., was exceeded in only four instances of the diseased gall bladder group.

SECRETIN-CHOLECYSTOKININ TEST IN CANCER OF BILE DUCTS.—All five patients with primary cancer of the bile ducts showed complete absence of bile throughout the test (Fig. 8).

SECRETIN-CHOLECYSTOKININ TEST IN CANCER OF PANCREAS.—Nineteen patients suffering from cancer of the pancreas showed varying responses (Fig. 8). Twelve showed negligible amounts of bile pigment due to severe biliary obstruction. In one of these patients the obstruction was overcome for half a minute, some four minutes after the pancreozymin injection was completed and a small amount of dark bile was recovered. Two patients, one with a cancer of the body and the other with a small cancer of the head of the pancreas, gave normal responses to both secretin and pancreozymin, while a third, in whom a cancer of the head completely obstructed the pancreatic duct, gave a normal cholecystokinetic response but the secretin test showed gall bladder dysfunction. At operation the sphincter of Oddi was found to be involved by the neoplasm, but the lumen of the common bile duct was patent. Two patients with a cancer of the body and one with

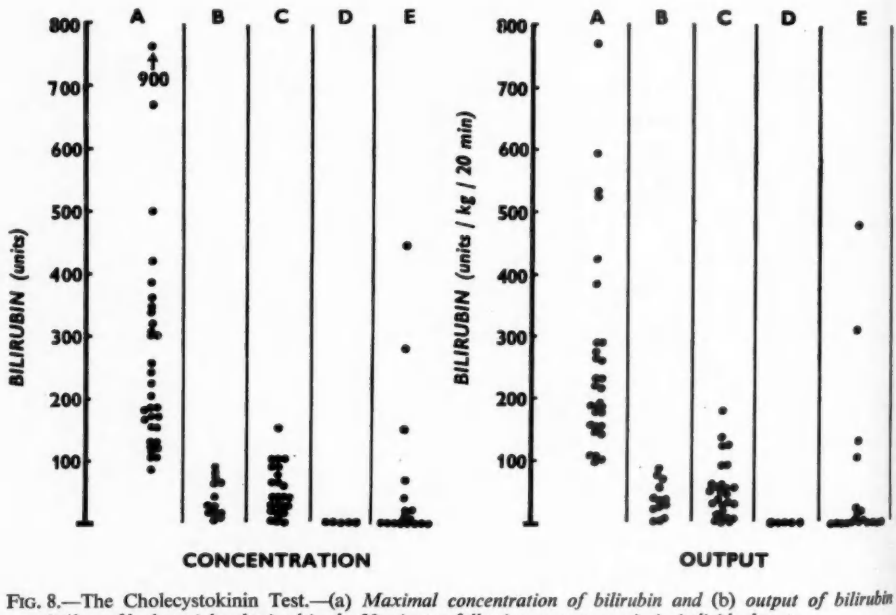



FIG. 8.—The Cholecystokinin Test.—(a) *Maximal concentration of bilirubin and* (b) *output of bilirubin units/kg. of body weight obtained in the 20 minutes following pancreozymin in individual tests.*

*A. Normal group (30 subjects).*
*B. Post-cholecystectomy (14).*
*C. Non-malignant gall bladder disease (27).*
*D. Cancer of bile ducts (5).*
*E. Cancer of pancreas (19).*

ampullary cancer gave responses suggesting a non-functioning gall bladder, though at operation the gall bladder appeared to be normal. A similar response was obtained in another patient with cancer of the head of the pancreas in whom the low output in many fractions and the presence of white bile in the gall bladder at operation one week later suggested that at the time of the test obstruction was nearly complete. The response obtained in this test probably reflects an intermediate stage between the normal response and complete obstruction of the duct by growth.

SECRETIN-CHOLECYSTOKININ TEST AFTER CHOLECYST-ENTEROSTOMY.—The response to secretin and pancreozymin in two patients in whom the gall bladder had been unastomosed to the duodenum was similar to that found in post-cholecystectomy cases. The output of bilirubin units in the 20 minutes following cholecystokinin was 45 and 37 units per kg. In a third patient with cholecystjejunostomy no bile was obtained.

## DISCUSSION

The cholecystokinin in pancreozymin preparations affords a means of contracting the gall bladder and obtaining gall bladder bile uncontaminated by stimulant. On this attribute a test of gall bladder function has been based.

The secretin test, cholecystography, and the cholecystokinin tests do not provide identical information about gall bladder function. In some respects these gall bladder tests overlap and in others they supplement each other. The secretin test depends on the flow of bile from the liver, the amount of pancreatic juice secreted, the integrity of the biliary ducts and sphincters, and the capacity of the gall bladder to accept bile. Cholecystography depends in addition on the ability of the gall bladder mucosa to concentrate the radio-opaque dye. The cholecystokinin test not only measures the ability of the gall bladder to concentrate bile but also the capacity of the gall bladder to contract and void concentrated bile into the duodenum. Put succinctly, the secretin test provides evidence of the capacity of the gall bladder to distend, cholecystography of its capacity to concentrate, and the cholecystokinin test of its capacity to contract and evacuate its contents. Discrepancies in the results of the three tests suggest that these three functions are not necessarily lost *pari passu* in gall bladder disease. In many instances, however, the clinical value of cholecystography lies not in indicating functional derangement, but in demonstrating the anatomical presence of non-radio-opaque gall stones in the gall bladder. Tests incorporating duodenal intubation prove of greatest value in these instances where the gall bladder may not be vizualized by cholecystography, either due to poor absorption of the dye from the bowel or in the presence of obstructive jaundice or following cholecystectomy. It is a prerequisite for the applicability of the cholecystokinin test as well as the secretin and oral cholecystography tests of gall bladder function that the liver should be able to excrete bile. In the presence of severe liver damage an abnormal response to the injection of cholecystokinin may be misleading.

The cholecystokinin test is not in strict terms a quantitative test since it is not known how far spontaneous contraction of the gall bladder during the preliminary period of fasting may have modified the concentration of bilirubin in the duodenal contents obtained when the gall bladder contracts in response to cholecystokinin. A second variable is the unknown quantity of dilute bile which enters the gall bladder from the liver in the 30 minutes following the injection of secretin, since secretin is a choleretic agent. The cholecystokinin test does, however, provide a semi-quantitative estimate of gall bladder function. In 28 of 29 normal individuals the maximum concentration of bilirubin after cholecystokinin exceeded 100 units. In the absence of the gall bladder the cholecystokinetic response rarely exceeded 80 units. Therefore when the maximum concentration of bile lies between 80 and 100 units the test has been adjudged to be doubtful. In complete obstruction of the bile ducts little bile pigment is recovered. Normal values are occasionally found where gall stones are present in the gall bladder, and yet gall bladder function is retained; in this context an abnormal test is of greater value clinically than a normal test. Used in conjunction with the secretin test of gall bladder function the cholecystokinin test is able to differentiate the variant of the normal response in which the gall bladder has to some extent contracted during the early stages of the secretin test from the type II response, and the acholic variant of the normal response when the gall bladder accepts all the liver bile secreted during the test from the type III response of the patient suffering from obstructive jaundice. In both these instances the cholecystokinin test indicates unequivocally the presence of a normal gall bladder.

A third variable is the considerable amount of pancreatic secretion which flows into the duodenum in response to secretin and pancreozymin and lowers the concentration of bilirubin. To compensate for this diluent effect of pancreatic secretion the output of bilirubin units has been calculated for the 20-minute period during which the gall bladder contracts in response to cholecystokinin and expressed

in terms of units per kilogram of body weight. In the group of 30 normal subjects the lowest output was 96 units per kg./20 minutes, while in the cholecystectomy group the highest output was 86 units per kg./20 minutes. Only four of 27 patients in the group with gall bladder disease exceeded the minimal figure of 96 units/kg. for the normal group and six patients with gall bladder disease exceeded the maximal figure of 86 units/kg. for the post-cholecystectomy group.

The different responses obtained in cancer of the pancreas reflect the varying degree of involvement of the common bile ducts and dysfunction of the biliary sphincter. Since the test has been used in conjunction with the secretin-pancreozymin test of pancreatic function, the cholecystokinin test is able in the presence of clinical jaundice to distinguish further the site of a lesion obstructing the biliary tract, particularly when obstruction is due either to primary cancer of the bile ducts or to primary cancer of the head of the pancreas. In some instances too the cholecystokinin test has indicated the presence of a non-malignant obstruction of the bile ducts due either to complete obstruction by stone or to ball valve obstruction by gall stones.

Finally cholecystokinin can provide bile from the gall bladder uncontaminated by stimulant for microscopic and cytological examination.

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# GASTRIC CYTODIAGNOSIS: A REVIEW AND APPRAISAL

BY

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This paper presents a careful appraisal of the technique of gastric cytodiagnosis, and sets out the criteria for diagnosis necessary to avoid false positive results.

By staining air-dried blood films with new dyes, Ehrlich (1891) showed the value of morphological criteria in accurate diagnosis of many haematological disorders. Similarly, in the field of exfoliative cytology, it was the development of a new staining technique by Papanicolaou (1942) that provided fresh opportunities and a stimulus for investigation, and the resulting practical application of a new aid in diagnosis. Weiss (1959) briefly surveyed the potentialities and limitations of cytodiagnostic methods; it is particularly the cytology of vaginal secretions and sputum that has become a routine and valuable test for cancer in many laboratories.

Like the cytology of other organs, gastric cytodiagnosis has a venerable history, with pioneer investigations by several continental pathologists at the end of the last century. The cytology of gastric washings has been the subject of much wider interest in the past 12 years. Nevertheless, the correct place of the investigation in patients suspected of gastric cancer, let alone as a screening method in patients with vague or minimal symptoms, remains uncertain. Unfortunately, many papers giving impressively high percentages of "true" positive diagnoses from washings done on patients later shown to have gastric cancer, omit information on the particular character of the growths, which are often diagnosed more quickly and easily by other methods. Some assessment of the contribution that gastric cytology can offer, in the context of information derived from clinical, radiological, and gastroscopic approaches, has recently been published (Burnett, MacFarlane, Scott Park, and Kay, 1960).

It may be predicted that the rewards of gastric cytology will be threefold. First, as impressively shown by Schade (1958, 1960), the method may provide the only means of diagnosis in certain "surface carcinomas" that are confined to the mucosa. Secondly, the presence of malignant cells in gastric washings will provide a firm diagnosis in a proportion of cases in which the radiological appearances are suspicious or inconclusive; but it will be seen that less reliance can be attached to negative washings in favouring benign lesions. Thirdly, cytological examination is useful, both as a curb to unnecessary investigation and as a guide to management in some patients with advanced malignant disease of the stomach.

Several investigators have advocated rather elaborate methods of collecting gastric material, or favour the use of special apparatus to scrape the mucosal surface of the stomach. In fact, it is likely that simple gastric lavage, carried out after an overnight fast, usually proves as rewarding as more complicated techniques and causes a minimum of discomfort to the patient. Details of the simple method of collection, and of Papanicolaou staining techniques are readily available (Staff of the Vincent Memorial Hospital, 1950; Schade, 1960). In brief, the stomach must be cleared of all food remnants; saline washings are then made through an intragastric rubber tube with multiple perforations with the patient in various positions; the aspirate is centrifuged with a minimum of delay, and the deposit is smeared and put into fixative while wet; the slides are carried through haematoxylin, followed by Papanicolaou's alcoholic staining solutions, and are finally cleared and mounted.

For malignant cells to be available it is naturally conditional that the growth should involve the mucosal lining of the stomach. It is rare for a localized submucosal cancer to be present, or for carcinomatous infiltrations to remain entirely deep to the mucosa. The presence of large necrotic tumours, or of pyloric obstruction, is much more commonly responsible for "false negative" results. In these circumstances it may not be possible to

collect aspirates that contain recognizable malignant cells.

Even with experience, the scanning and interpretation of smears is exacting in time. In practice it is found that at least three hours should be set aside for the collection, preparation, and examination of material from a patient, and longer may be required before a search is pronounced negative with certainty.

It is unlikely that cytodiagnosis will be recommended for the routine diagnosis of gastric cancer but, for the investigation of selected patients, it will undoubtedly find a place. An intention of this article is to give an idea of its possibilities and limitations; it is hoped that a judgment will be possible on the validity of some of the evidence used in reaching cytological diagnoses.

## The Origin of Cells in Gastric Washings

Cells collected from the stomach present a greater challenge to the resourcefulness of the exfoliative cytologist than material from other sites, by virtue of the fact that the stomach acts as a temporary reservoir for secretions from various sources. Cells may originate from respiratory, oral, nasal, or oesophageal mucous membranes; they exfoliate from the gastric mucosa sparsely in health, but profusely in various local and diffuse abnormalities; or, rarely, they may be derived from the duodenum or biliary tract, carried by the retrograde flow of juices.

Few attempts have been made to correlate the cytological appearances seen in smears with the histological sections of "parent" tissue taken from specimens after operation. Schade (1959) has made a contribution to this basic task.

## Available Illustrations of Gastric Cytology

Attention will be drawn to the publications on gastric cytodiagnosis, in which helpful illustrations accompany the texts.

The *Cytologic Diagnosis of Cancer*, by the staff of the Vincent Memorial Hospital (1950), illustrates effectively many of the characteristic appearances in exfoliative cytology. Low-power views are given, with parallel illustrations in high magnification, of particular groups of cells. A lack of clarity in reproducing the photomicrographs is compensated for by drawings of the same fields. There is little consideration given to the many deviations from normal that may be seen in benign conditions, and only a few representative malignant cells from the stomach are depicted.

Papanicolaou's *Atlas of Exfoliative Cytology* (1954, Supplement 1956) offers a major source of reference on the subject, and at present acts as the archives for illustrations of cytological material. Kodachrome photomicrographs and drawings in colour are portrayed. The drawings are beautifully executed and minute attention has been given to detail. It is inevitable, however, that the separation of the cells from their backgrounds and the addition by the artist of a dimension of depth, should tend to give a slightly artificial, even stylized quality, to some of the drawings. There are no less than 132 illustrations of the cytology of the digestive system. Additions have been made as new material has become available, with the result that there is no systematic presentation. As most of the material illustrated is derived from specimens obtained by abrasive gastric balloons, there has been comparative neglect of the non-malignant cytology of the stomach.

Henning and Witte (1957) illustrate their *Atlas der gastroenterologischen Cytodiagnostik* with an excellent series of photomicrographs. Their material was collected by a special device, the "*Zelltupfsonde*", enabling cells to be obtained by sponging the mucosa, and their studies are particularly valuable in showing the cellular changes that take place in atrophic gastritis. They also depict chief or parietal cells, which appear to resist the effects of simple lavage, for they are extremely rare in aspirates.

Richer (1956) has written a valuable and critical account of his experience of gastric washings in diagnosis, and he includes 12 photomicrographs in his paper. It is particularly noteworthy that these include cells showing atypical but non-malignant changes, which he found difficult to interpret with certainty from some patients with atropic gastritis or healing gastric ulcers.

Bruinsma (1957) reports his studies on a small series of patients with carcinoma of the stomach, in whom he used the "gastric balloon". The accompanying photomicrographs, especially those in colour, are realistic and of high quality, the majority representing malignant cell groups.

Schade (1960) has published a treatise on gastric cytology of great importance, in which he traces the historical development of the investigation, mentions the various techniques of collection that have been advocated, and presents the results of his experience derived from cytological studies on 2,443 patients since 1954. By the use of simple lavage and examination of smears he has obtained highly impressive results, claiming an overall accuracy of 96% in a group of 522 of these patients in whom the diagnosis was proved by laparotomy or resection. There were a further 36 patients in whom the diagnosis was established at operation, but whose gastric aspirates had been deemed unsuitable for

cytological examination. Twenty-four of these had carcinoma. It might be presumed that some had advanced growth or obstruction, in which circumstances reasonably clear washings are notoriously difficult to obtain. In the 264 patients in whom a benign condition was found at resection (mainly peptic ulceration), and from whom suitable aspirates were obtained, 13 "false positives" occurred, constituting about 5% of the total. The greater percentage of "false positive" diagnoses in the benign group than "false negative" results in the cancer group is explained by Schade on the basis of atypical but non-malignant epithelium, in mucosa surrounding ulcers.

The most remarkable feature of Schade's work is the report of 16 surface cancers in patients not suspected of malignancy on clinical or radiological grounds; the histology of several of these tumours is illustrated convincingly. These patients came to operation, apparently, only as a result of positive cytodiagnosis, obtained during a survey investigation on gastritis. It is implied that such localized early carcinomas may come to the attention of clinicians on account of symptoms produced by chronic gastritis, which is thought frequently to precede rather than merely accompany malignant change.

The choice and quality of photomicrographs in Schade's book should receive comment. To those with some experience of exfoliative cytology, most of the illustrations of malignant cells in smears will carry conviction. They convey, particularly, those criteria of malignancy that apply to abnormal arrangements and relationships within cell clusters, but there is often lack of clarity in displaying the inherent features of malignancy of the cells. It is disappointing not to have specific representation of some of the cells that led to "false positive" reports. It is in this group that the criteria of malignancy are put to their most severe test, and with the knowledge of the final histological diagnosis it would have been possible to appreciate some of the difficulties that may arise in making interpretations.

## Characteristics of Cells Collected from the Stomach

Classification of cell types encountered must be based on the probable sites of origin of cells that have been shed into the stomach, though it will be realized that the major relevance of special features present in the various cells lies in the way in which these resemble or differ from the cytological characteristics of malignancy. It is with this in mind that the descriptions are presented. Schade (1960) has correctly stressed the additional importance of the "background" in smears—blood, leucocytes, goblet cells, meat fibres, bacteria—and there is no doubt that such features can provide valuable supporting evidence in a cytological opinion.

Squamous Epithelial Cells.—Squames from oral and oesophageal epithelial surfaces are nearly always the most prominent cells in gastric washings. A simple division into superficial squamous cells and parabasal cells is sufficient.

(1) *Superficial squamous cells* are easily recognized (Fig. 1). They are large and flat, with sharp, rather squared-off edges; the cytoplasm is usually pink, but may be basophilic and take up a light blue tint; granular and hyaline material is often present in the cytoplasm; nuclei are oval, centrally placed, and stain blue, or become small and densely pyknotic in the most superficial cells.

(2) *Parabasal cells* (Fig. 2) are comparatively infrequent but may occasionally lead to confusion. The cytoplasm is a fairly deep blue; the nucleus is usually eccentric, and has a sharp nuclear membrane. The nuclei may be hyperchromatic and contain granular chromatin and one or more prominent nuclei, thus reflecting an "active" appearance, due to the fact that they are making good the loss, from wear and tear, of the superficial layers of epithelium.

Cells from Respiratory Epithelium.—Ciliated columnar epithelial cells, which range from tall and delicate structures, to plump, broad, multinucleated forms, are desquamated from bronchial or nasal mucous membranes. They are distinctive so long as they remain well preserved (Figs. 3 and 4). They are not very common in gastric washings, but may be carried to the stomach in swallowed sputum, or by the passage of a naso-oesophageal tube. The nuclei may be slightly irregular, densely staining and overlap one another. If these cells are present in clumps and are devoid of most of their cytoplasm, they may arouse false suspicions of malignancy.

*Histiocytes or Macrophages.*—(1) Respiratory histiocytes (Fig. 5) are constantly present in sputum and therefore frequent in gastric washings. They are usually easily identified and as a rule distinguishable from the macrophage elements of the gastrointestinal tract. They have a round or slightly oval outline; cytoplasm is greeny-blue, foamy, and typically, though not constantly, contains black particles of carbon; nuclei are purplish blue, oval or kidney shaped, and placed eccentrically. Cells may contain two or more nuclei. The cells themselves are often to be found in ranks, strung out in strands of mucus.

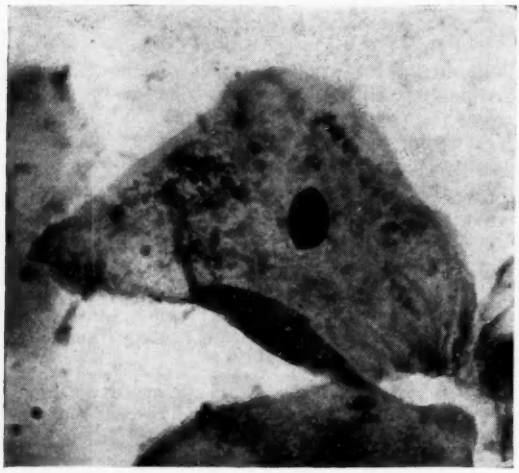

FIG. 1.—*Squamous epithelial cells from superficial layers.*

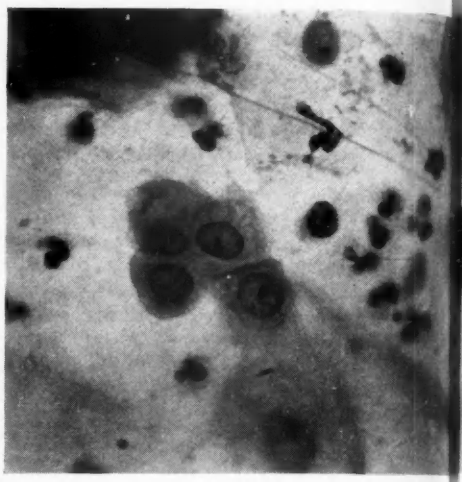

FIG. 2.—*Squamous epithelial cells: clump of four cells from basal layers, with superficial squames. Polmorphs. Bacteria.*

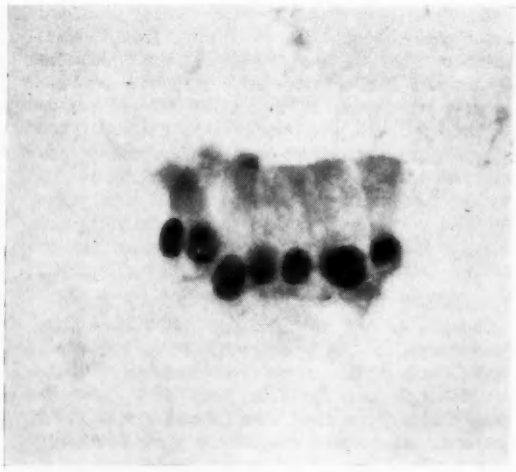

FIG. 3.—*Respiratory epithelium. Well-preserved, columnar, ciliated cells.*

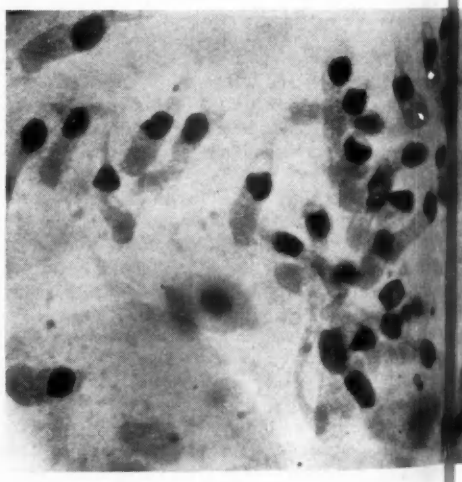

FIG. 4.—*Respiratory epithelium.*

*The approximate magnification of cells represented in the photomicrographs is* × *850.*

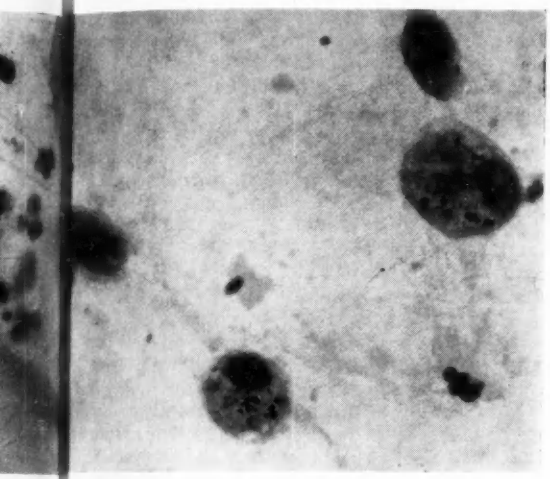

FIG. 5.—*Histiocytes in swallowed sputum; "dust cells", with carbon particle inclusions.*

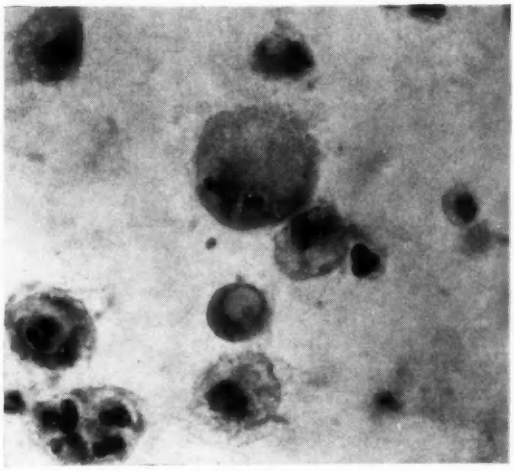

FIG. 6.—*Histiocytes from stomach; droplet and leucocyte inclusions.*

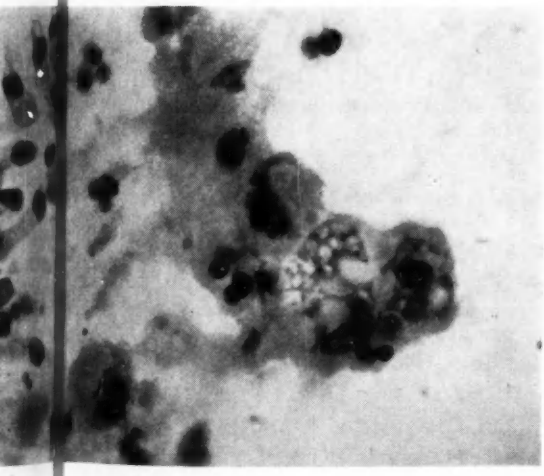

FIG. 7.—*Histiocytes from stomach. Accretion of cells with ingested refractile material.*

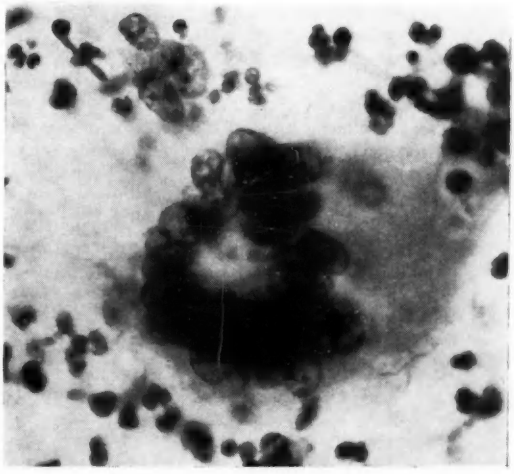

FIG. 8.—*Multinucleated histiocyte. "Foreign body giant cell."*

(2) Histiocytes of gastrointestinal origin (Fig. 6) are not normally seen, but may appear in large numbers in washings from patients with gastric ulcer, atrophic gastritis, or carcinoma. Their general configuration is the same as those of respiratory origin, but differences in detail are usually recognizable. The cell borders are often indistinct; the cytoplasm is frequently foamy, sometimes containing large vacuoles, but lacks carbon particle inclusions. The staining property of the cytoplasm is variable, and it does not assume the greeny-blue hue usual in respiratory histiocytes. Nuclei tend to have less sharply defined borders and to be less regular in shape. Phagocytosis of leucocytes is very common, and the histiocytes, at times, appear crammed with polymorphonuclear remnants, which tend to displace and distort the nuclei.

*Giant Histiocytes.*—Occasionally foreign body giant cells (Fig. 8) are to be found in smears from gastric washings, usually in the presence of extensive gastric tumours. They contain many nuclei, which are often disposed peripherally.

*Cells Derived from Blood.*—(1) Red blood cells are common in saline gastric washings, and it is important to realize that visible blood in the centrifuge deposit is a fairly frequent finding in non-malignant conditions. This, of course, contrasts with the frequently sinister import of blood in a gastric test meal; the trauma from jets of saline in a washing often seems sufficient to produce mucosal haemorrhage, in the absence of malignant disease, though the mucosa is obviously abnormal in many non-malignant conditions.

(2) Polymorphonuclear leucocytes are sparse in the normal fasting stomach, but are often present as a dense background in smears from patients with carcinoma, ulcer, or gastritis. They are to be seen infiltrating the abnormal mucosa in atrophic gastritis, and enclosed in macrophages, and sometimes in malignant cells (Fig. 18). Their state of preservation varies and probably depends on the degree of acidity. Occasionally clumps of purple dots are present, and represent fragmented nuclear lobes.

(3) *Round Cells.*—Lymphocytes seldom predominate in smears, but their presence, in conjunction with abnormal forms, might suggest the diagnosis of lymphosarcoma of the stomach (Klayman, Kirsner, and Palmer, 1955). Plasma cells are common in atrophic gastritis, and they are easily recognized by their eccentric, "cartwheel" nuclei, and fairly abundant, often reddish cytoplasm.

CELLS FROM GASTRIC EPITHELIUM.—The columnar epithelium which lines the stomach does not exfoliate readily in health, and the cells when present show considerable constancy of shape and size, though their states of preservation vary. Large groups of cells are usually seen end on. They then show polygonal outlines, most cells having distinct borders, and particularly from the basal surface, they show a honeycomb-like appearance (Fig. 9). Cells scattered in small groups or singly often appear from their lateral aspects, showing rectangular outlines, faintly blue cytoplasm, and unipolar nuclei which contain finely granular material. The cells are particularly susceptible to the cytolytic action of gastric juice, which often denudes them, so that only cytoplasmic remnants cling to the nuclei, or only naked nuclei remain.

Striking changes in the cells from the stomach with atrophic gastritis may appear, and it is these that are most likely to cause diagnostic difficulties, by mimicking those seen in true malignant cells. Although the clinical relevance of atrophic gastritis may be argued, there has been greater appreciation of the frequency of the histological change, since the work of Doig and Wood (1958), using the flexible biopsy tube. Though gradations exist, a distinction can be made between the three histological pictures of superficial and atrophic gastritis, and complete gastric atophy. Atrophic gastritis may itself be "zonal", near lesions such as gastric ulcer or carcinoma, or near an anastomotic stoma; or it may be "diffuse". No real estimate of the extent of the mucosal change can be gauged from gastric washing. From the affected areas the superficial layer of epithelium exfoliates profusely, the cells often appearing in syncytial sheets. The cells are plumper and more circular than normal, and show varying degrees of anisokaryosis, nucleolar prominence, and overlapping of nuclei (Figs. 10, 11, and 12). In addition, goblet cells, each containing a distended vacuole that may compress the nucleus, are often present, and indicate that areas of mucosa have altered to the intestinal pattern. Abundant polymorphs, some of which permeate the abnormal epithelium, macrophages and plasma cells, often contribute further to the picture.

Brief reference will be made to alterations in the gastric epithelium observed in patients with pernicious anaemia. It is known that there is nuclear enlargement of cells from several epithelial surfaces (Boddington and Spriggs, 1959). Rubin (1955) mentioned two distinct types of gastric epithelial cell, the "large bland columnar cell" and the "active cell". The active cells are well preserved and show chromatin clumping and large nuclei (Fig. 15), but it is now clear that they are not confined to patients with pernicious anaemia, and may be present with chronic atrophic gastritis (Henning and Witte, 1957).

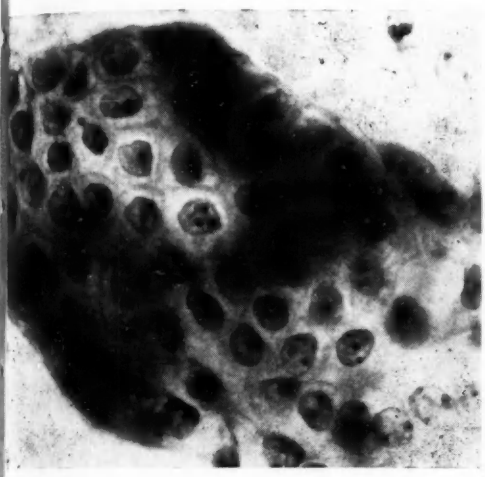

FIG. 9.—*Gastric surface epithelium. "Honeycomb" appearance with clear definition of cell borders.*

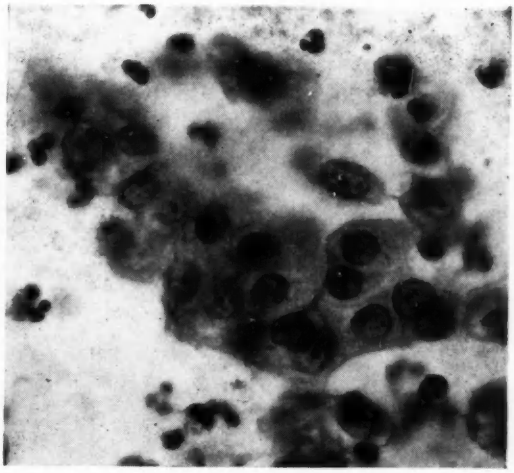

FIG. 10.—*Atrophic gastritis. Syncytial appearance of mucosal cells.*

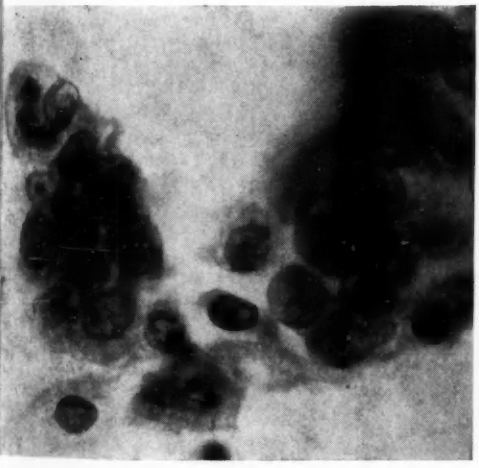

FIG. 11.—*Atrophic gastritis. Nuclear variation in shape and size, "overlapping", nucleolar prominence. Leucocyte inclusions in epithelium.*

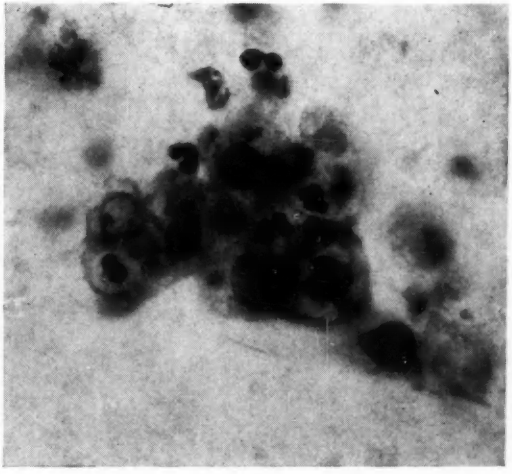

FIG. 12.—*Atrophic gastritis. Clump of epithelial cells with indistinct borders and polymorph inclusions.*

*The approximate magnification of cells represented in the photomicrographs is × 850.*

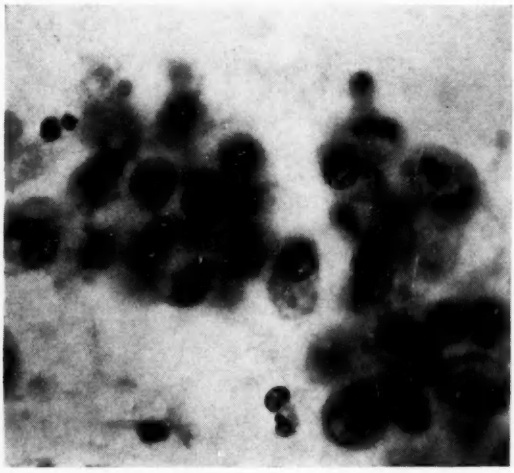

FIG. 13.—*Gastric epithelial cells showing nuclear irregularity, nucleolar prominence, and leucocyte inclusions.*

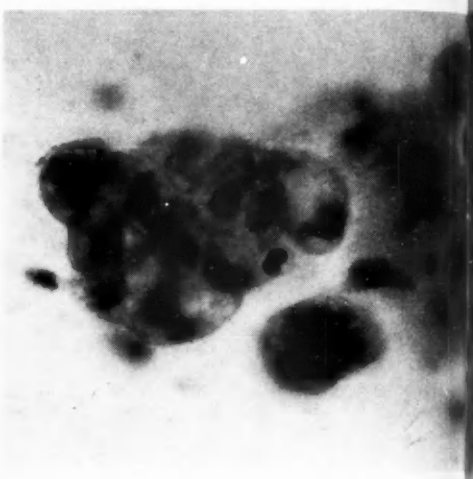

FIG. 14.—*Cluster of closely packed gastric epithelial cells, two showing features of "goblet cells". No cancer at operation.*

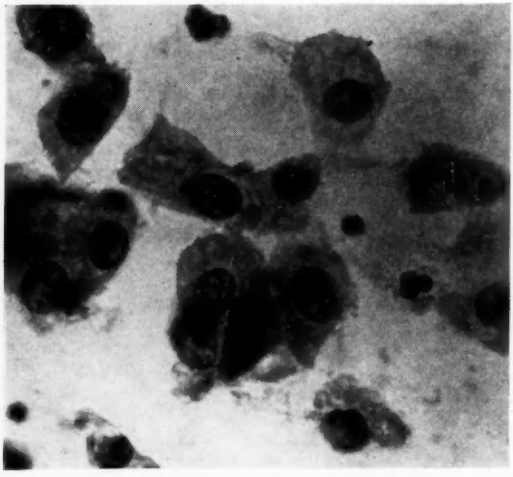

FIG. 15.—*Gastric columnar cells which are plump, contain vacuolated cytoplasm, and have "active" nuclei. Patient had achlorhydria; laparotomy was negative.*

FIG. 16.—*Single columnar carcinoma cell; impressive clumping of chromatin in the nucleus.*

*The approximate magnification of cells represented in the photomicrographs is × 850.*

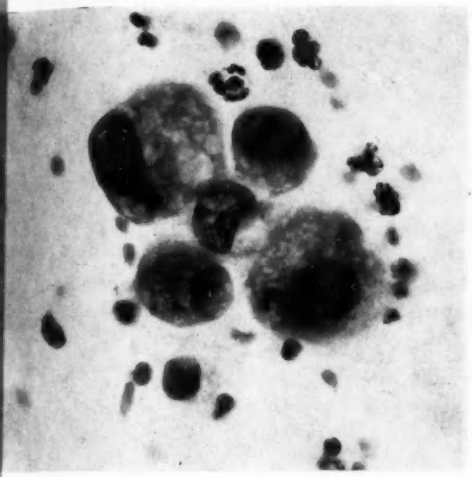

FIG. 17.—*Group of carcinoma cells from a patient with "leather bottle" stomach. Note large size of cells, impressively vacuolated cytoplasm, and gross nuclear abnormalities.*

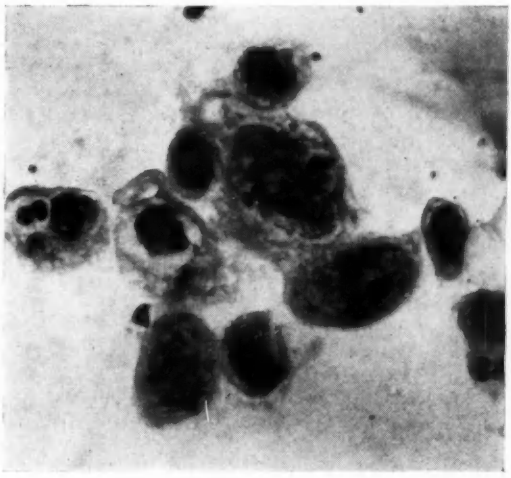

FIG. 18.—*Undifferentiated gastric carcinoma cells. Note giant nucleoli and cytoplasmic inclusions of leucocytes.*

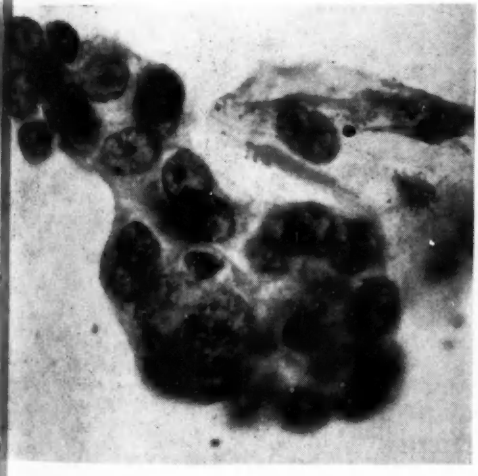

FIG. 19.—*Undifferentiated gastric carcinoma cells, including a giant malignant nucleus.*

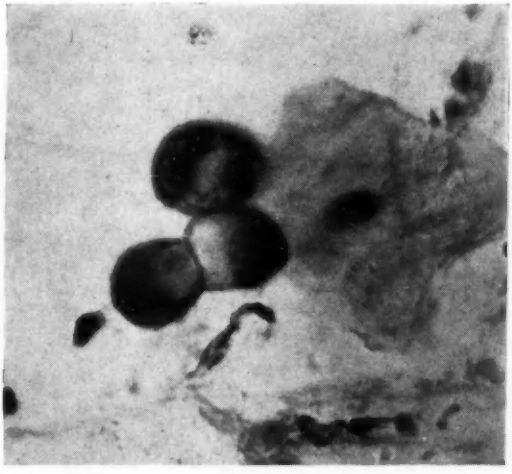

FIG. 20.—*Mucus-secreting carcinoma cells.*

FIG. 21.—*Two small carcinoma cells; superficial squamous cell; polymorphs. Note abnormal nucleo-cytoplasmic ratio and hyperchromasia shown in malignant cells.*

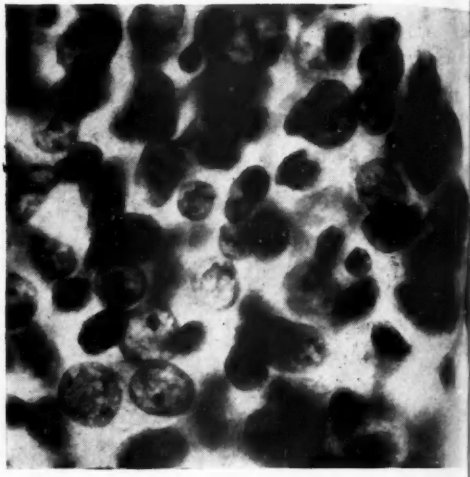

FIG. 22.—*Sheet of undifferentiated carcinoma cells, illustrating nuclear variation and "overlapping". Operation specimen showed mucosal malignant change in a gastric polyp.*

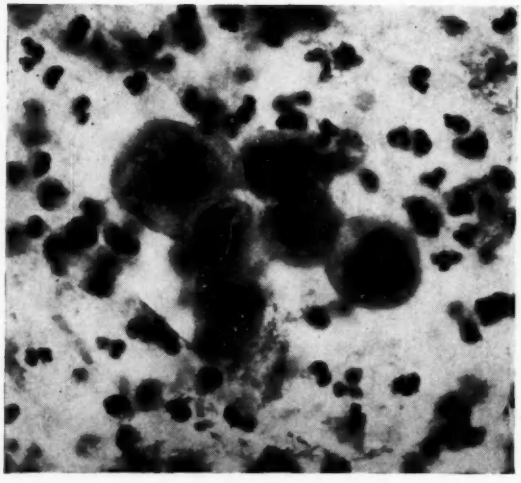

FIG. 23.—*Group of carcinoma cells against a dense background of polymorphs. Note grossly abnormal nuclear features, including lobulation indentation and multiple nucleoli.*

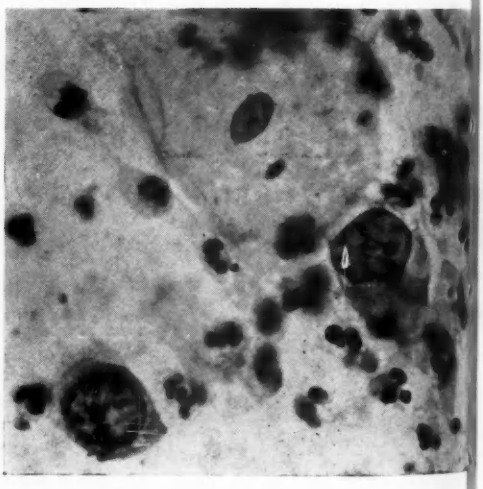

FIG. 24.—*Two carcinoma cells; superficial squame; polymorphs. Note thickening of nuclear membrane in lower malignant cell.*

*The approximate magnification of cells represented in the photomicrographs is* × *850.*

In giving cytological verdicts on patients with pernicious anaemia caution is clearly demanded, but the definite criteria of malignancy become no less reliable or valid.

### Cytological Criteria of Malignancy in Gastric Carcinoma

Papanicolaou (1954) gives the most useful general analysis of the criteria of malignancy in cytology; Schade (1956, 1960) lays emphasis on certain characteristics which have frequent application to material from the stomach. Some of the criteria will be recapitulated, but the most convincing persuasion may come from examination of the photomicrographs of malignant cells (Figs. 16 to 24). Cells vary both in number and prominence of malignant features that they display, and some of the non-malignant conditions that may cause confusion have been mentioned. The most notable are atrophic gastritis and healing gastric ulcers. A small number of cases show these borderline criteria, and the fact that difficulties exist should not be used as an argument against the validity of cytological diagnosis when cells show incontrovertible stigmata of malignancy. Extreme caution is necessary before pronouncing a doubtful smear as malignant; Richer (1956) wisely pleads: "Mieux vaut être timoré qu'imprudent."

The criteria of malignancy most frequently applicable in gastric cytodiagnosis are:

I. Nuclear changes suggesting malignancy: (1) increase in nucleo-cytoplasmic ratio (Fig. 21); (2) hyperchromasia (Fig. 20); (3) abnormal chromatin patterns, including irregular clumping (Fig. 16), lobulation, indentation, and furrowing (Fig. 23); (4) nuclear gigantism (Fig. 19); (5) variations in nuclear size—anisokaryosis (Figs. 17 and 18); (6) enlargement, or an increase in number, of nucleoli (Figs. 18 and 23); (7) thickening of the nuclear membrane (Fig. 24); (8) crowding and overlapping of nuclei (Fig. 22).

II. Cytoplasmic changes (though providing little specific help in deciding on malignancy): (1) excessive vacuolation (Fig. 17) or mucus secretion, indicative of adenocarcinoma (Fig. 20); (2) leucocyte inclusions (Fig. 18).

III. Criteria derived from whole cells, and cell groups: (1) tendency to clump, without any regularity of pattern; (2) indistinct cell borders, or merging of cytoplasm (Figs. 18 and 19); (3) increase in size and anisocytosis (Figs. 17 and 18).

### Conclusion

Clinicians frequently enquire as to the possible value of gastric cytology in investigating individual patients. Many papers have been written giving results of cytological investigations on series of patients with suspected or proven gastric cancer but, with few exceptions, there are inadequate data and illustrations to enable the reader to judge the basis upon which the cytological conclusions have been reached. Ultimately, the only valid test for the usefulness of gastric cytodiagnosis is to apply the investigation to patients suspected of carcinoma of the stomach, with adequate comparison of histological material obtained later from the same patients. Before undertaking such work, the investigator will want information on the reliability of the criteria that have been applied to exfoliated cells. There is little doubt that, once the cytologist has acquired sufficient special experience, the technique offers a valuable diagnostic approach which, though usually supplementary, may occasionally be vitally useful and provide an emphatically positive answer in the presence of equivocal, or rarely negative results, by other approaches. Firmly positive reports will probably prove possible, from single washings, in about 70% patients with gastric carcinoma. It is clear that undue reliance should not be placed on negative cytology in excluding carcinoma.

Many contributions on gastric cytodiagnosis have been marred by a significant number of false positive results, which can only mean an acceptance of criteria of malignancy that are insufficiently rigid, and a refusal to admit that, in a small proportion of cases, it is impossible to give a categorical answer.

An attempt has been made to survey briefly the subject of gastric cytodiagnosis. It will be inferred that the availability of the technique is not likely to be limited by any complexity of procedure, nor by reluctance of patients to accept it, but by the time and special experience available from a cytologist. Reference has been made particularly to those publications on gastric cytology that provide illustrations which are most likely to prove of value for comparative purposes. The remarkable reluctance of most authors to illustrate material that has led them to give false-positive diagnoses is mentioned. Certain cells encountered in gastric washings are described, and attention is given to the criteria used in the cytological diagnosis of gastric malignancy. Illustrations have been chosen to complement the descriptions and enable judgment to be made on the acceptability of the criteria.

I am grateful to the physicians and surgeons of the London Hospital for allowing me access to their patients. I am indebted to Mr. A. J. King, A.R.P.S., A.I.B.P., for the skill and meticulous care he has shown in preparing the photomicrographs. The cost of the photographs and

materials was met by a grant from the London Hospital Research Fund.

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# THE JUNE (1960) ISSUE

The June (1960) issue contains the following papers:—

Crohn's Disease (Regional Enteritis) of the Large Intestine and its Distinction from Ulcerative Colitis. H. E. LOCKHART-MUMMERY and B. C. MORSON.

Volvulus of the Caecum. GEOFFREY CHAMBERLAIN.

A Test of Pancreatic Function in Man Based on the Analysis of Duodenal Contents after Administration of Secretin and Pancreozymin. P. BURTON, D. G. EVANS, A. A. HARPER, HENRY T. HOWAT, S. OLEESKY, J. E. SCOTT, and H. VARLEY.

Serum Amylase and Serum Lipase Levels in Man after Administration of Secretin and Pancreozymin. P. BURTON, ELIZABETH M. HAMMOND, A. A. HARPER, HENRY T. HOWAT, J. E. SCOTT, and H. VARLEY.

Leucine Aminopeptidase with Special Reference to Ulcerative Colitis. L. J. WITTS and S. W. PERRY.

Effect of Glucagon on Gastric Secretion in Man. A. G. MELROSE.

Effect of Glucagon on Gastric Secretion in the Dog. S. D. CLARKE, D. W. NEILL, and R. B. WELBOURN.

Partial Gastrectomy for Peptic Ulcer. V. S. BROOKES, J. A. H. WATERHOUSE, and P. A. THORN.

A Report of Two Cases of Whipple's Disease Diagnosed by Peroral Small Intestinal Biopsy. C. J. DICKINSON, M. HARTOG, and MARGOT SHINER.

Hepatic Necrosis Due to Marsilid. C. F. MCCARTHY and M. R. SHERIDAN.

Smoking and the Alimentary Tract: A Review. R. S. PACKARD.

*Present-day Techniques*

Use of Bisacodyl in Preparation of the Bowels for a Barium Enema. J. G. SOWERBUTTS.

Gastro-intestinal Blood Loss Measured by Radioactive Chromium. A. D. CAMERON.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

*Gut*, 1960, **1**, 217.

# AN ASSESSMENT OF PREDNISONE, SALAZOPYRIN, AND TOPICAL HYDROCORTISONE HEMISUCCINATE USED AS OUT-PATIENT TREATMENT FOR ULCERATIVE COLITIS

BY

J. E. LENNARD-JONES,* A. J. LONGMORE, A. C. NEWELL, C. W. E. WILSON, and F. AVERY JONES

*From St. Mark's Hospital, London*

Two consecutive trials of out-patient treatment for mild cases of active ulcerative colitis are described. In the first trial oral prednisone gave significantly better results than a placebo. In the second trial "salazopyrin" gave final results approaching those of prednisone, although over a longer time and with a higher incidence of unpleasant side-effects, but topical hydrocortisone gave disappointing results, probably because the technique of administration was not suitable for ordinary out-patient use.

Controlled trials have shown that three treatments—oral cortisone (Truelove and Witts, 1955), topical hydrocortisone hemisuccinate sodium (Truelove, 1958b; Watkinson, 1958), and topical prednisolone 21-phosphate (Matts, 1960)—favourably influence the course of active ulcerative colitis. By comparative trial with cortisone, corticotrophin is also known to be effective (Truelove and Witts, 1959). Much information (Svartz, 1956; Moertel and Bargen, 1959) has now been accumulated indicating that "salazopyrin"† is another effective drug, though a prospective controlled trial is so far lacking.

During the years 1956-59, three remedies—oral prednisone, topical hydrocortisone, and "salazopyrin"—have been assessed in the medical out-patient clinic at St. Mark's Hospital. The investigation was done in two stages, each a separate trial, and preliminary results of both have been reported (Newell and Avery Jones, 1958; Lennard-Jones, Longmore, and Avery Jones, 1960). In the first stage, during 1956 and 1957, the effectiveness of oral prednisone was compared with that of calcium lactate, assuming this to be an inert substance. This trial established prednisone as an effective treatment. In the second stage, during 1958 and 1959, prednisone was used as a standard with which "salazopyrin" and hydrocortisone hemisuccinate retention enemata therapy could be compared.

## Method of Study

Selection of Patients and Allocation of Treatments.—The patients selected for these trials were suffering from active ulcerative colitis involving part or all of the colon distal to the splenic flexure. All were treated as out-patients, all suffered little or no systemic upset from their disease, and all were eligible for any of the treatments under trial. In the first stage of the trial 19 patients whose hospital number was even were given prednisone and 18 patients with an odd number were given calcium lactate. The second stage of the trial included 60 patients, 20 treated with each of three remedies. After patients had been included in this stage, treatment was allocated by blindly drawing a slip from a box containing 60 slips, 20 marked with each treatment. The 97 trials of treatment in the two stages involved 92 different patients. No patient was included twice in either stage of the trial but five patients were included in both the first and second stages.

Comparability of the Treatment Groups.—By the criteria for selection of patients the severity of the disease should be comparable in the different treatment groups. The data on patients' symptoms shown in Table I suggest that this is so. Fewer first attacks of disease were treated in the calcium lactate and topical hydrocortisone groups. It is doubtful if this affects the final results as none of the patients treated during a first attack were benefited by calcium lactate and only one by topical hydrocortisone.

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† Salicylazosulphapyridine.

TABLE I

COMPARABILITY OF THE TREATMENT GROUPS

| | No. of Patients | Mean Age | Males | Treated for First Attack | Treated for Relapse | Symptoms | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Diarrhoea and Bleeding | Bleeding Only | Diarrhoea Only |
| Prednisone (1) | 19 | 38 (S.D. 12) | 8 | 7 | 12 | 11 | 8 | 0 |
| Calcium lactate | 18 | 41 (S.D. 11) | 7 | 3 | 15 | 8 | 10 | 0 |
| Prednisone† (2) | 12 | 40 (S.D. 8) | 4 | 3 | 9 | 4 | 8 | 0 |
| Salazopyrin | 20 | 38 (S.D. 16) | 7 | 10 | 10 | 11 | 8 | 1 |
| Prednisone (3) | 20 | 44 (S.D. 14) | 8 | 8 | 12 | 13 | 7 | 0 |
| Topical hydrocortisone | 20 | 45 (S.D. 17) | 12 | 5 | 15 | 13 | 7 | 0 |

† After failure of calcium lactate.

ASSESSMENT OF RESULTS.—Patients' symptoms were recorded at each visit and subsequently classified as:—

"No change or worse" } Compared with the symptoms before treatment and judged from the patient's statements about frequency of bowel action and bleeding. (A general sense of well-being alone was not accepted as indicating improvement.)
"Improved" }

"No symptoms" Normal bowel actions without bleeding or discharge. (An occasional streak of blood on a normal stool was accepted as freedom from symptoms.)

Sigmoidoscopy was performed at each visit and the appearances were classified as:—

"Active" =oedematous, *friable* mucosa, no granularity
"Moderately active" =moist *granular*, *friable* mucosa
"Inactive" =dry, granular, *not friable* mucosa
"Normal" =*vascular pattern* visible throughout

Improvement or deterioration was recognized if the appearance on one visit was in a different category from that on another.

"Remission" of the disease is defined as freedom from symptoms combined with the finding of an inactive or, rarely, normal mucosa on sigmoidoscopy. Freedom from symptoms with an active mucosa or vice versa did not constitute "remission". "Improvement" on overall assessment usually indicated improvement in both symptoms and sigmoidoscopic appearance.

TABLE II

DURATION OF TREATMENT AND TOTAL DOSE OF DRUG UNTIL REMISSION OR UNTIL END OF TREATMENT

*Stage 1:*

| | Prednisone | | | Calcium Lactate | | | Prednisone after Failure of Calcium Lactate | | |
|---|---|---|---|---|---|---|---|---|---|
| | Remission | Improved | No Benefit | Remission | Improved | No Benefit | Remission | Improved | No Benefit |
| Number of patients | 13 | 4 | 2 | 3 | 3 | 12 | 9 | — | 3 |
| Weeks of treatment (mean and range) | 3·5 (1-10) | 11·3 (6-20) | 4 (3-5) | 8 (4-14) | 10 (3-20) | 4·4 (1-15) | 5·7 (1-12) | — | 8·7 (8-9) |
| Total dose (g.) (mean and range) | 1·0 (0·4-2·4) | 2·2 (1·5-3·4) | 1·4 (1·3-1·4) | — — | — — | — — | 1·3 (0·4-2·2) | — | 2·0 (1·5-2·6) |

*Stage 2:*

| | Salazopyrin | | | Prednisone | | | Topical Hydrocortisone | | |
|---|---|---|---|---|---|---|---|---|---|
| | Remission | Improved | No Benefit | Remission | Improved | No Benefit | Remission | Improved | No Benefit |
| Number of patients | 8 | 5 | 7 | 11 | 5 | 4 | 3 | 5 | 12 |
| Weeks of treatment (mean and range) | 8·5 (2-16) | 24 (3-52) | 7 (0-21) | 3·9 (3-8) | 9·8 (3-19) | 5·5 (5-6) | 3·7 (3-5) | 11·4 (3-21) | 3 (0-8) |
| Total dose (g.) (mean and range) | 154 (20-308) | 310 (54-532) | 104 (0-354) | 1·1 (0·9-1·9) | 1·8 (0·9-3·1) | 1·3 (1·2-1·6) | 2·6 (2·1-3·5) | 5·5 (2·1-8·7) | 2·2 (0·5-6) |

The mean time between the start of treatment and remission of the disease was significantly ($P = < 0{\cdot}02$, $t = 2{\cdot}79$, $n = 17$) longer with "salazopyrin" (8·5 weeks) than with prednisone (3·9 weeks). The first assessment was made at three or four weeks; nine out of 11 remissions during prednisone treatment occurred by this time, compared with two out of eight remissions during "salazopyrin" therapy.

## Results

STAGE 1: COMPARISON BETWEEN PREDNISONE AND CALCIUM LACTATE.—In this trial the treatment determined by the patient's hospital number was given for three to four weeks; both doctor and patient knew which treatment was given. If at the end of this time there was no improvement after treatment with calcium lactate, prednisone was substituted; calcium lactate was not substituted if prednisone failed. In one case treatment with calcium lactate was stopped and prednisone substituted after one week and in another case after two weeks, because of worsening of the illness. If a patient's condition improved, treatment was continued until full remission was achieved, or until the maximum benefit had apparently resulted, when it was withdrawn. Prednisone was given in a dose of 40 to 60 mg. daily for the first week and then the dose was slowly reduced; calcium lactate was given in a dose of 1·3 g. daily.

The overall results of treatment are shown in Fig. 1. Of the 19 patients treated initially with prednisone, remission was achieved in 13, nine of them being in remission within three weeks of starting treatment. In the corresponding group given calcium lactate remission was achieved in three out of 18 patients. Only two out of 19 patients received no benefit from prednisone whereas 12 out of 18 patients received no benefit from calcium lactate. These 12 patients in whom calcium lactate had failed were given prednisone and remission occurred in nine of them. Although numbers are small, remission perhaps occurred earlier among those treated with prednisone than among those treated with calcium lactate (Table II). The difference between the number of remissions which occurred with prednisone and with calcium lactate given as first treatments is such as would have occurred by chance less than once in 100 times.

STAGE 2: COMPARISON BETWEEN SALAZOPYRIN, HYDROCORTISONE RETENTION ENEMATA, AND PREDNISONE.—Preliminary results of this trial with the technique and doses used have already been reported (Lennard-Jones *et al.*, 1960). Briefly, after a patient had been included in the trial, one of the three treatments was allocated by random selection. Again, both doctor and patient knew which treatment was given. Patients were usually seen after treatment for three weeks. If there was no improvement by this time the treatment was considered a failure and the trial ended. If there was definite or possible improvement the treatment was continued in reduced dosage until remission or apparent maximum benefit was achieved, and it was then slowly withdrawn. For the first three weeks, "salazopyrin" was given in a total dose of 4 g. daily; hydrocortisone (as hemisuccinate sodium), 100 mg. freshly dissolved in 150 ml. of normal saline as a retention enema nightly, using the modified blood transfusion set described by Truelove (1958a); and prednisone in a total dose of 60 mg. daily for the first week, 45 mg. daily for the second week, and 30 mg. daily for the third week.

After the first three weeks the greatest number of patients was free of symptoms after prednisone, the fewest after hydrocortisone retention enemata; "salazopyrin" gave intermediate results. The final assessment of the three treatments is shown in Fig. 2. Of the 20 patients treated with each remedy, remission occurred in 11 patients given prednisone (seven of them within three weeks of starting treatment), eight given "salazopyrin", and three treated with hydrocortisone retention enemata. Remission was achieved significantly ($P = <0{\cdot}02$) sooner with prednisone than with "salazopyrin" (Table II). The difference between the number of remissions which occurred during treatment with prednisone and with topical hydrocortisone is such as would have occurred by chance less than once in 50 times. The number of remissions which occurred during treatment with "salazopyrin" is not significantly different from the number which occurred during calcium lactate, topical hydrocortisone, or prednisone therapy.

SIDE-EFFECTS FROM TREATMENT.—Of the 51 patients treated with prednisone during the two stages of the trial, 17 complained of side-effects, two of whom found it necessary to reduce the dose during the first three weeks. None of the side-effects were serious and all disappeared when the dose was reduced; we are not aware of any long-term harm from steroid treatment among these patients, all but two of whom have been followed for more than six months after ending treatment. The symptoms complained of were mooning of the face (7), dyspepsia (5), acne (4), gain in weight (2), palpitations (2), flushes (1), and syncopal attacks (1).

Two patients treated with calcium lactate developed side-effects, heartburn (1) and "pimples" (1).

Twelve patients out of the 20 treated with "salazopyrin" complained of unpleasant side-effects, namely, nausea (4), anorexia (3), vomiting (2), malaise (2), diarrhoea (1), and skin rash (1). Three patients (accounting for three out of five failures of the treatment) could not take the drug even in small doses, five others could only take a reduced dose (Fig. 2). We have not observed any haematological complications.

One patient complained of colic after the retention enemata.

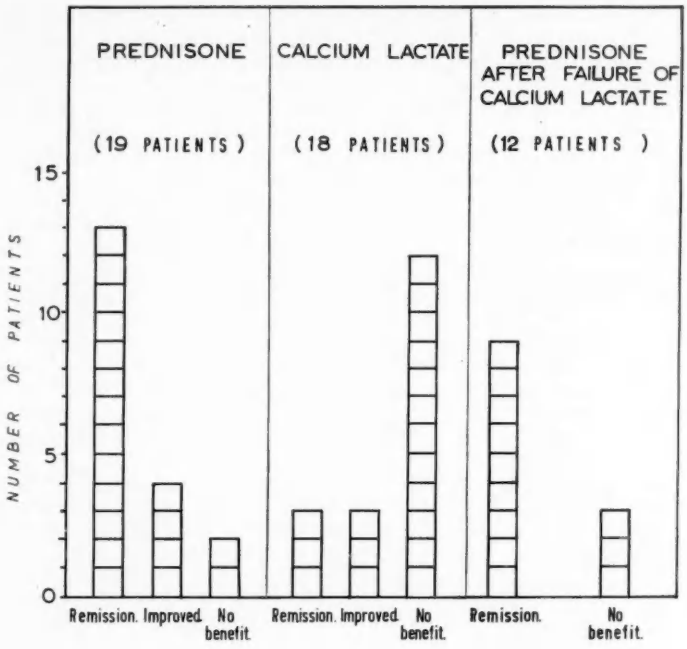


FIG. 1.—*The results of treatment with prednisone and calcium lactate. The number of patients in whom remission of the disease occurred was significantly greater during initial treatment with prednisone than during treatment with calcium lactate* ($\chi^2_c = 10{\cdot}1$, $n = 1$, $P = <0{\cdot}01$).

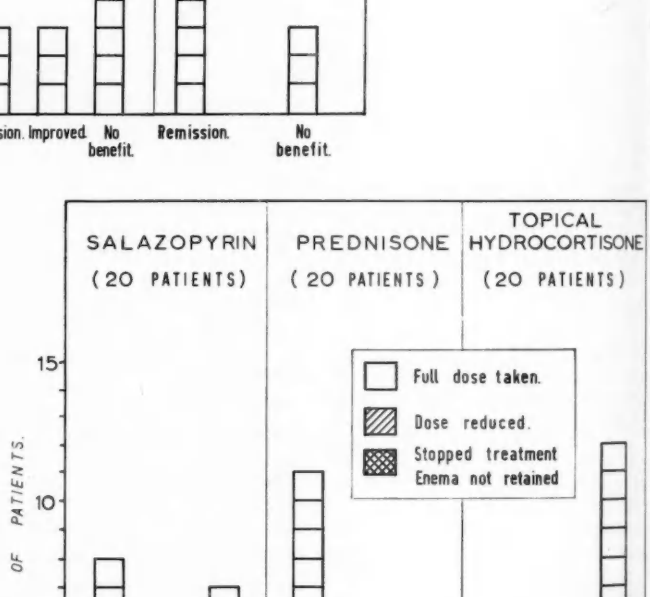


FIG. 2.—*The results of treatment with "salazopyrin", prednisone, and topical hydrocortisone. The number of patients in whom remission of the disease occurred was significantly greater during treatment with prednisone than during treatment with topical hydrocortisone* ($\chi^2_c = 6{\cdot}6$, $n = 1$, $P = <0{\cdot}02$).

RELAPSE RATE AFTER REMISSION ACHIEVED.—Nineteen of the 33 patients in remission after treatment with prednisone relapsed during the next six months (follow-up incomplete in two patients). The illness in four became active again as treatment was withdrawn at daily doses of 15, 10, 5, and 5 mg. respectively. Of the 12 patients in remission at six months, four patients relapsed during the next six months and four more between one and two years; only three patients have remained in remission for more than two years (one patient has remained in remission for 21 months; follow-up for two years is incomplete). The numbers in remission after the other treatments are too small to draw valid conclusions about the rate of relapse.

## DISCUSSION

The usefulness of cortisone in ulcerative colitis has been firmly established by the Medical Research Council trial (Truelove and Witts, 1955). We know of no other controlled trials of oral corticosteroid therapy in this disease. The present trial differs from the M.R.C. trial in several ways. First, all the patients suffered from mild, though active, disease and were treated as out-patients. Second, a different drug, prednisone, was used, specially selected for its anti-inflammatory effect. Third, patients were treated with initial high doses followed by a rapid reduction. Even though a double-blind trial was not performed, the results appear to establish the usefulness of prednisone as out-patient treatment; no lasting harmful effects of treatment occurred with the régime described. The remission rate in the M.R.C. trial among mild cases was 75% and among cases of moderate severity 31% at the end of six weeks. Our cases would fall into these two categories and the remission rate of 65% in this series appears comparable.

The effectiveness of "salazopyrin" as treatment for ulcerative colitis has been described by many authors (Svartz, 1956; Moertel and Bargen, 1959), but there has been a notable dearth of contemporary controlled observations. The present investigation suggests that "salazopyrin" is a useful drug. Its main advantage is that it does not cause adrenal suppression or other potential hazards of corticosteroid therapy. It suffers the disadvantages of relatively slow action compared with prednisone and of frequently causing unpleasant side-effects, perhaps especially noticeable by out-patients who feel otherwise well.

The results of hydrocortisone retention enema therapy in this series were disappointing. The technique used was cumbersome and complicated, suitable more for hospital than out-patient use. No attempt was made to select patients for this treatment who were adaptable, intelligent, and without aversion to the idea of self-administration of enemata. Five out of 20 patients failed to retain the enemata (one because of diarrhoea and three because of inability to carry out the treatment unaided), but even among the remainder results were unsatisfactory. We believe that topical corticosteroid treatment can be very effective as Truelove (1958b) and Watkinson (1958) have shown. Techniques such as the disposable enema bags described by Flavell Matts (1960) should make this type of therapy more convenient for out-patient use. Hydrocortisone given rectally is absorbed to some extent (Nabarro, Moxham, Walker, and Slater, 1957) and it seems worth pointing out that large total doses of hydrocortisone may be given during maintenance treatment with retention enemata; one of our patients received 8·7 g. over 21 weeks.

From this trial we conclude that oral prednisone brings about rapid remission of the disease in a high proportion of cases and that "salazopyrin" probably brings about remission almost as frequently, though more slowly. Since systemic corticosteroid treatment is potentially dangerous we suggest that it is best in most cases to start treatment with "salazopyrin" or topical corticosteroid treatment, using one of the newer techniques. The high relapse rate after successful treatment with prednisone shows that the greatest need at present is for a drug which will prevent relapse once remission is achieved.

## SUMMARY

(1) A controlled trial against a placebo demonstrated the effectiveness of oral prednisone as an out-patient treatment for active left-sided ulcerative colitis.

(2) In a comparative trial, performed consecutively, prednisone gave the best results; "salazopyrin" gave final results approaching those of prednisone, but more slowly and with a higher incidence of side-effects; topical hydrocortisone gave disappointing results, probably largely due to the technique of administration used. Statistical evidence for the effectiveness of "salazopyrin" was not obtained. The results from prednisone were significantly better than those from topical hydrocortisone.

(3) Remission occurred in 33 out of 51 patients treated with prednisone during the two stages of the trial, often within three weeks of starting treatment. Relapse of the illness occurred among more than half of these patients during the next six months.

No dangerous side-effects resulted from the treatment.

We thank the consultant staff of the hospital for referring patients included in this study, members of the Records and Research Departments for their help, and Glaxo Laboratories for the hydrocortisone hemisuccinate sodium used in the trial. Expenses of the study were met from a research grant by the Board of Governors of the Hammersmith and St. Mark's group of hospitals.

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# A CLINICAL AND STATISTICAL STUDY OF THE EFFECT OF GASTROJEJUNOSTOMY ON HUMAN GASTRIC SECRETION

BY

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By a statistical study using the Kay augmented histamine test it has been shown that performing a gastrojejunostomy has no fundamental effect on gastric secretion and that the post-operative differences are due entirely to reflux and/or loss through the stoma.

We have previously reported the effect of vagotomy with gastrojejunostomy, antrectomy, and of antrectomy combined with vagotomy on human gastric secretion (Gillespie, Clark, Kay, and Tankel, 1960). More recently our interest has been focused on the effect of vagotomy and gastrojejunostomy on gastric secretion with a view to estimating the effect of the vagotomy. However, in comparing pre-operative and post-operative results, it is difficult to evaluate how much of the alterations in volume or acid output should be ascribed to the presence of the gastrojejunostomy alone.

The literature on the effect of gastrojejunostomy on gastric secretion, which has been reviewed by Ivy, Grossman, and Bachrach (1950), is inconclusive. Some workers reported no effect on secretion, others a moderate reduction. Moreover, experiments were not performed in a readily comparable way nor were results given in such reproducible units as can be obtained from the augmented histamine test (Kay, 1953).

We have again studied this problem from two points of view. First, we wished to record the effect of gastrojejunostomy on gastric secretion as judged by the volumes and total acid outputs of the spontaneous secretion and the augmented histamine response. Secondly, if any alteration did occur, it was clearly desirable to determine if this could be explained by alteration of the secretory activity of the parietal cells or simply by reflux or loss through the stoma.

## METHOD

Male patients with duodenal ulcer were selected for study. All had clinical and radiological evidence of pyloric stenosis and most were over 50 years of age, these two factors being felt to justify treatment by gastrojejunostomy alone. In severe stenosis the presence of undigested food occasionally rendered aspiration difficult. These patients were not included in the series, leaving 17 patients to be studied in detail.

The posterior gastrojejunostomy was made with the stoma placed at the most dependent part of the greater curvature of the stomach.

Augmented histamine tests as described by Kay (1953) were carried out twice pre-operatively and on two occasions seven to 10 days post-operatively. The patients were fasted overnight and care was taken in the placing of the intragastric tube so that the stomach could be completely emptied by continuous suction with an electric suction pump. The patency of the tube was verified at frequent intervals by the injection of a little air. Spontaneous secretion was measured over a period of one hour. The augmented histamine secretion was collected during the second and third 15-minute periods following the histamine injection, this half hour being the period of maximal stimulation. Volume in millilitres and total acid output in milliequivalents HCl were measured. In order that direct comparisons could be made between the rates of spontaneous secretion and the augmented histamine response, the values for spontaneous secretion over one hour were halved. The means of the two pre-operative readings were then compared with the means of the post-operative readings in each case. The regression equations were calculated to four decimal places and then rounded off to two decimal places.

## RESULTS

SPONTANEOUS SECRETION.—The volumes are shown in Table I. There is a large variation from patient to patient in the actual volumes, both in the pre-operative and the post-operative tests. In all but two cases the post-operative volume is higher. That this is due to reflux of bile and duodenal juice

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TABLE I

EFFECT OF GASTROJEJUNOSTOMY ON GASTRIC SECRETION*

| Patient No. | Pre-operative | | | Post-operative | | |
|---|---|---|---|---|---|---|
| | Spontaneous Secretion | Augmented Histamine Response | Difference | Spontaneous Secretion | Augmented Histamine Response | Difference |
| 1 | 31·25 | 155·0 | 123·75 | 35·25 | 122·0 | 86·75 |
| 2 | 70·25 | 236·5 | 166·25 | 147·50 | 336·0 | 188·50 |
| 3 | 24·75 | 92·5 | 67·75 | 37·50 | 87·5 | 50·00 |
| 4 | 21·00 | 78·5 | 57·50 | 27·50 | 71·5 | 44·00 |
| 5 | 25·50 | 104·5 | 79·00 | 41·25 | 112·0 | 70·75 |
| 6 | 34·25 | 191·0 | 156·75 | 103·50 | 185·5 | 82·00 |
| 7 | 45·00 | 173·5 | 128·50 | 64·50 | 154·0 | 89·50 |
| 8 | 49·50 | 115·0 | 65·50 | 42·00 | 83·0 | 41·00 |
| 9 | 24·50 | 173·0 | 148·50 | 74·00 | 214·0 | 140·00 |
| 10 | 11·75 | 122·0 | 110·25 | 26·00 | 87·0 | 61·00 |
| 11 | 77·00 | 222·0 | 145·00 | 84·50 | 266·0 | 181·50 |
| 12 | 69·00 | 215·5 | 146·50 | 74·25 | 176·0 | 101·75 |
| 13 | 67·25 | 178·0 | 110·75 | 58·00 | 169·5 | 111·50 |
| 14 | 34·50 | 175·0 | 140·50 | 73·00 | 174·0 | 101·00 |
| 15 | 37·50 | 126·5 | 89·00 | 49·00 | 111·5 | 62·50 |
| 16 | 21·00 | 80·0 | 59·00 | 43·75 | 93·0 | 49·25 |
| 17 | 50·50 | 179·5 | 129·00 | 78·00 | 117·0 | 39·00 |
| Mean ± S.D. | 40·85 20·05 | 154·00 50·06 | 113·15 36·71 | 62·32 30·99 | 150·56 71·42 | 88·24 45·87 |

* Volume is expressed in ml./half hour.

is suggested by the fact that there was gross bile staining of the juice in all but six of the 17 patients (Nos. 1, 4, 7, 10, 12, 14) though it must be noted that these six patients also had a greater output post-operatively, in two cases more than 100% greater.

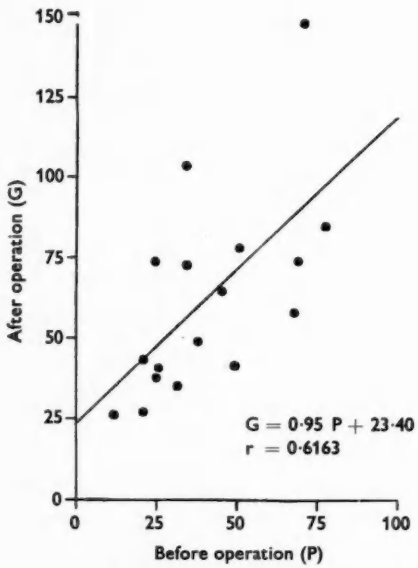


FIG. 1.—*The relationship between the pre-operative and post-operative spontaneous secretory volumes in ml./half hour.*

Fig. 1 shows the pre-operative volumes (P) plotted against the corresponding post-operative volume (G). The correlation between the pre-operative and post-operative values is significant ($r = 0{\cdot}6163$, $P < 0{\cdot}01$). This permits us to draw the line which best fits the data. The regression of G on P is given by

$G = 0{\cdot}95\,P + 23{\cdot}40$ (equation 1) (standard error of the estimate $= \pm 25{\cdot}20$).

The factor 0·95 is very close to 1·00 and is not significantly different from it, so that the formula may be reduced to

$G = P + 21{\cdot}47$† (equation 1a)

This suggests that the post-operative volume is identical with the pre-operative volume with the addition of a constant = 21·47 ml. It will be argued later that this constant, which is significantly different from 0 ($t = 3{\cdot}51$; $P < 0{\cdot}01$), is a measure of the inflow of bile and pancreatic juice less any loss that takes place after gastrojejunostomy. The size of the standard error is not unexpected since there is bound to be a good deal of variation in these factors from patient to patient.

The total outputs of acid are shown in Table II. Following gastrojejunostomy the output was reduced in nine patients (in four cases to zero), raised in seven patients, and unaltered in the patient with achlorhydria.

†This is obtained as follows:

$G = 0{\cdot}9527P + 23{\cdot}4030$

(Equation 1 extended to four places of decimals)

$= P - 0{\cdot}0473P + 23{\cdot}4030$

$= P - 0{\cdot}0473 \times 40{\cdot}8530 + 23{\cdot}4030$

(Since the mean value of $P = 40{\cdot}8530$)

$= P - 1{\cdot}9323 + 23{\cdot}4030$

$= P + 21{\cdot}4707$

TABLE II

EFFECT OF GASTROJEJUNOSTOMY ON GASTRIC SECRETION*

| Patient No. | Pre-operative | | | Post-operative | | |
|---|---|---|---|---|---|---|
| | Spontaneous Secretion | Augmented Histamine Response | Difference | Spontaneous Secretion | Augmented Histamine Response | Difference |
| 1 | 1·17 | 17·82 | 16·65 | 0·82 | 12·92 | 12·10 |
| 2 | 5·18 | 34·18 | 29·00 | 7·08 | 37·51 | 30·43 |
| 3 | 0·53 | 7·69 | 7·16 | 1·10 | 5·43 | 4·33 |
| 4 | 0·96 | 8·94 | 7·98 | 0·71 | 5·13 | 4·42 |
| 5 | 0·28 | 4·82 | 4·54 | 0·00 | 3·64 | 3·64 |
| 6 | 0·90 | 21·29 | 20·39 | 5·14 | 18·36 | 13·22 |
| 7 | 2·29 | 18·34 | 16·05 | 2·81 | 10·21 | 7·40 |
| 8 | 1·87 | 11·73 | 9·86 | 2·05 | 11·81 | 9·76 |
| 9 | 0·37 | 18·76 | 18·39 | 0·00 | 14·29 | 14·29 |
| 10 | 0·00 | 12·11 | 12·11 | 0·00 | 1·99 | 1·99 |
| 11 | 4·38 | 23·03 | 18·65 | 1·94 | 24·20 | 22·26 |
| 12 | 3·60 | 23·95 | 20·35 | 1·22 | 16·44 | 15·22 |
| 13 | 4·29 | 21·15 | 16·86 | 2·98 | 14·49 | 11·51 |
| 14 | 1·66 | 20·90 | 19·24 | 3·31 | 17·71 | 14·40 |
| 15 | 0·88 | 15·53 | 14·65 | 0·00 | 3·30 | 3·30 |
| 16 | 0·82 | 7·60 | 6·78 | 0·94 | 3·91 | 2·97 |
| 17 | 3·16 | 21·22 | 18·06 | 0·00 | 3·70 | 3·70 |
| Mean ± S.D. | 1·90 ± 1·63 | 17·00 ± 7·48 | 15·10 ± 6·30 | 1·77 ± 1·99 | 12·06 ± 9·28 | 10·29 ± 7·73 |

* Acid output is expressed in mEq./ half hour.

Fig. 2 shows the pre-operative acid outputs (P) plotted against the post-operative outputs (G). Once again there is a significant correlation ($r = 0.5479$; $0.05 > P > 0.02$) between the pre-operative and post-operative results. The regression of G on P is given by

$G = 0.67P + 0.49$ (equation 2) (standard error of the estimate $= \pm 1.72$).

In this case the factor 0·67 does not appear to be close to 1·00 but is actually not significantly different from it ($t = 0.86$; $0.5 > P > 0.4$), and since the mean value of $P = 1.90$ the formula may be reduced to

$G = P - 0.13$ (equation 2a)

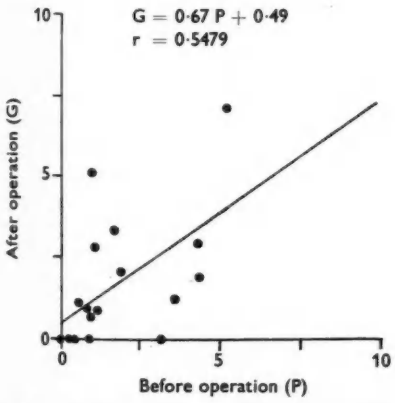


FIG. 2.—*The relationship between pre-operative and post-operative spontaneous acid outputs (mEq./half hour).*

Using the same argument as before this would suggest that there was no significant difference between the pre-operative and post-operative outputs and little neutralization as suggested by a low constant (0·13) which is not significantly different from 0 ($t = 0.31$; $0.8 > P > 0.7$). This will be discussed more fully later.

AUGMENTED HISTAMINE RESPONSE.—Table I shows the effect of simple gastrojejunostomy on the volume of the augmented histamine response. Although the post-operative volume exceeded the pre-operative volume in five patients, the changes were small and in only two cases were they greater than 30% in either direction. Bile was present post-operatively in 10 patients compared with two pre-operatively. Of these 10 patients, six showed a decrease and four an increase in volume after gastrojejunostomy, so that losses from the stomach occurred as well as reflux into the stomach.

Fig. 3 shows the pre-operative volumes (P) plotted against the post-operative volumes (G). Once again there is a significant correlation ($r = 0.8625$; $P < 0.01$). The regression of G on P is given by

$G = 1.24P - 39.89$ (equation 3) (standard error of the estimate $= \pm 37.33$).

The factor 1·24 is not significantly different from 1·00 ($t = 1.26$; $0.3 > P > 0.2$) and the equation may, therefore, be reduced to

$G = P - 3.44$ (equation 3a) since $\bar{P} = 154.0$. This equation suggests very little change in the volume of the augmented histamine response following gastrojejunostomy. This is in contrast to the spontaneous secretion where there was an average increase of 21·47 ml. In order to exclude the

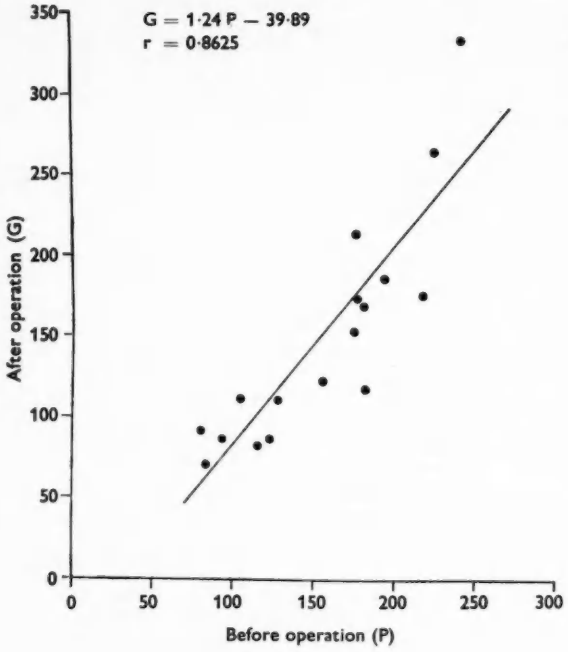


FIG. 3.—*The relationship between the pre-operative and post-operative augmented histamine volume (ml./half hour).*

possibility that this was due to the difference between the rates of spontaneous secretion and of the augmented histamine response, the spontaneous secretion was subtracted from the augmented histamine response to give the increase in volume due to histamine, and compared with the corresponding post-operative volume. The correlation was significant ($r = 0{\cdot}7302$; $P < 0{\cdot}01$) and Fig. 4 shows the graph and regression line which is given by

$G = 0{\cdot}91P - 14{\cdot}99$ (equation 4) (standard error of the estimate $= \pm 32{\cdot}37$).

Again the factor 0·91 is not significantly different from 1·00 and the formula may be reduced to

$G = P - 24{\cdot}91$ (equation 4a)

This suggests that, on balance, gastrojejunostomy produces a reduction in the volume by a constant amount probably due to loss through the stoma.

The total outputs of acid pre-operatively and post-operatively are also shown in Table II. There is a reduction in all but three patients and in these patients the increases were small (0·7, 5·1, and 9·7% respectively). There was a wide range in the reductions produced, as high as 83·6%. In general, the largest reductions took place in the patients showing reflux of bile but two of the three with an increase in acid output also showed a reflux of bile.

Fig. 5 shows the pre-operative acid outputs (P) plotted against the post-operative outputs (G). The correlation is significant ($r = 0{\cdot}8341$; $P < 0{\cdot}01$) and the regression line which gives the best fit is given by

$G = 1{\cdot}03P - 5{\cdot}53$ (equation 5) (standard error of the estimate $\pm 5{\cdot}29$).

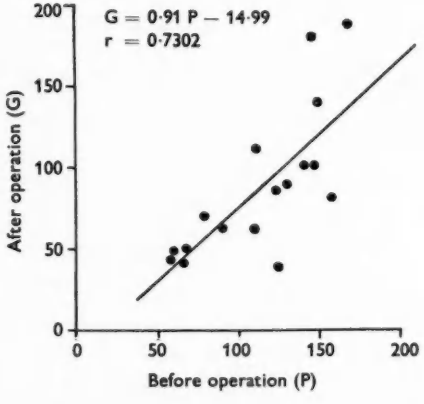


FIG. 4.—*The relationship between the pre-operative and post-operative volumes (ml./half hour) when the spontaneous secretion is subtracted from the augmented histamine response.*

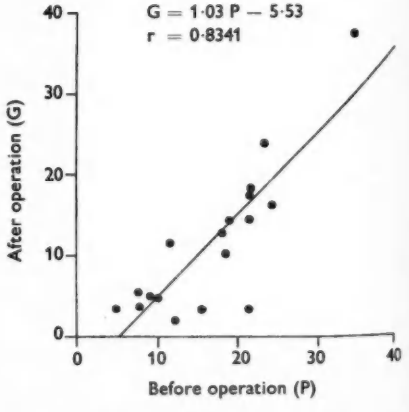


FIG. 5.—*The relationship between the pre-operative and post-operative augmented histamine acid outputs (acid output in mEq./half hour).*

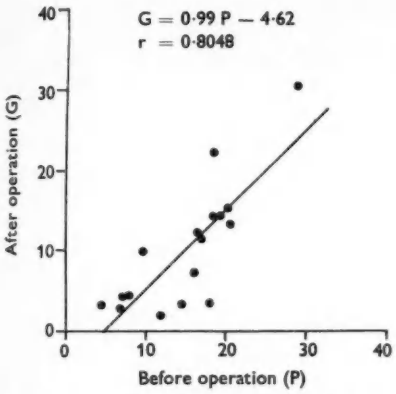


FIG. 6.—*The relationship between the pre-operative and post-operative acid outputs when the spontaneous secretion is subtracted from the augmented histamine response (acid output in mEq./half hour).*

The factor 1·03 is very close to unity and is not significantly different from it. The formula may, therefore, be reduced to

$$G = P - 4{\cdot}94 \text{ (equation 5a)}$$

These formulae also suggest that the pre-operative and post-operative outputs are identical except for a constant reduction of 4·94 mEq. due to neutralization and/or loss through the stoma. The constant (4·94) is not identical with the constant found in the spontaneous secretion (0·13) and is significantly different from it ($t = 3{\cdot}78$; $P < 0{\cdot}01$). To exclude any factor due to the difference in secretory rates between the augmented histamine response and spontaneous secretion, the spontaneous acid output was subtracted from the augmented histamine response as already described for volume.

Fig. 6 shows these results graphed against each other. The correlation is significant ($r = 0{\cdot}8048$; $P < 0{\cdot}01$) and the regression line is given by

$G = 0{\cdot}99\ P - 4{\cdot}62$ (equation 6) (standard error of the estimate $= \pm 4{\cdot}74$).

The factor 0·99 is very close to 1·00 and is not significantly different from it so that the formula may be reduced to

$$G = P - 4{\cdot}81 \text{ (equation 6a).}$$

This formula is almost identical with equation 5a,

$$G = P - 4{\cdot}94$$

There is now no significant difference between the constants.

RELATIONSHIP BETWEEN SPONTANEOUS SECRETION AND AUGMENTED HISTAMINE RESPONSE.—In the course of examining the above data it was decided to examine the relationship between spontaneous secretion and the augmented histamine response to see if the relationship was changed in any way by gastrojejunostomy.

There is a significant correlation between the pre-operative spontaneous and augmented histamine volumes ($r = 0{\cdot}7687$; $P < 0{\cdot}01$). Fig. 7 shows both sets of data graphed with their corresponding regression lines. The pre-operative regression line of H on S is given by

$$H = 1{\cdot}91\ S + 75{\cdot}97 \text{ (equation 7)}$$

where H = volume of augmented histamine response in ml./half hour

and S = volume of spontaneous secretion in ml./half hour (standard error of the estimate $= \pm 32{\cdot}90$).

The corresponding post-operative correlation was also significant ($r = 0{\cdot}8941$; $P < 0{\cdot}01$) and the regression line is given by

$H = 2{\cdot}06\ S + 22{\cdot}12$ (equation 8) (standard error of the estimate $\pm 33{\cdot}03$).

These two formulae have almost identical regression coefficients, 1·91 and 2·06. The regression lines are, therefore, almost parallel. The difference between

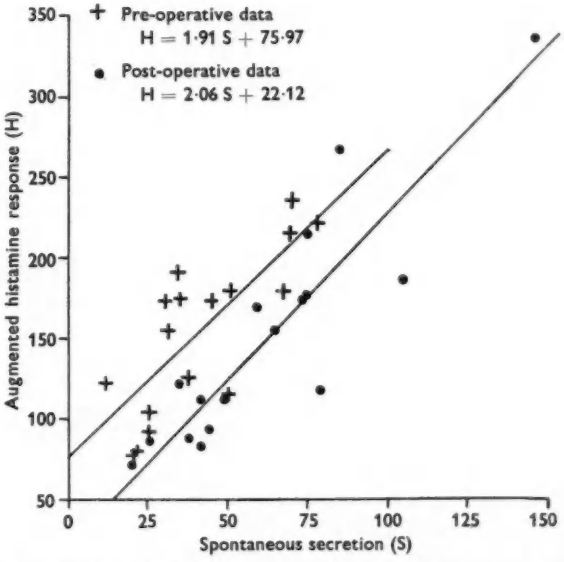


FIG. 7.—*Comparison between the pre-operative and post-operative relationships between the spontaneous and augmented histamine volumes in ml./half hour.*

them is 46·11 when S = 51·59 (the overall mean value of S). This difference is significant (t = 5·75; P < 0·01). Thus operation has reduced the volume by an amount which tends to be constant, and in this calculation has a mean value of 46·11. This compares with the figure of 24·91 in equation 4a and is significantly higher than it (t = 2·70, 0·02>P> 0·01). The reason for this is not clear.

When the spontaneous and augmented histamine acid outputs are compared there is again a significant correlation pre-operatively (r = 0·7775; P < 0·01) and post-operatively (r = 0·8183; P < 0·01). Fig. 8 shows both sets of data with the corresponding regression lines. The pre-operative regression line is given by

H = 3·58 S + 10·21 (equation 9) (standard error of the estimate = ± 4·86)

and the post-operative regression line is given by

H = 3·81 S + 5·33 (equation 10) (standard error of the estimate = ± 5·51).

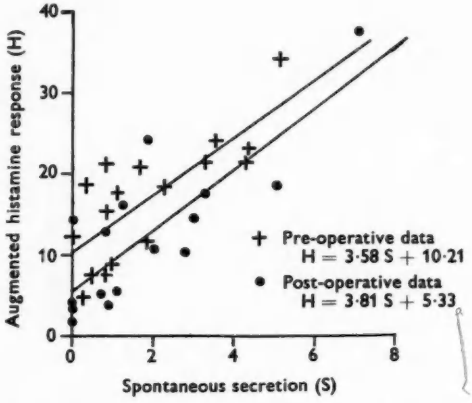


FIG. 8.—*Comparison between the pre-operative and post-operative relationships between the spontaneous and augmented histamine acid output (mEq./half hour).*

Once again the two formulae are almost identical with each other except with respect to the constants 10·21 and 5·33 and so are almost parallel on the graph. The difference between them is 4·46 when S = 1·83 (the overall mean value of S). This constant is not significantly different from the constant 4·81 obtained in equation 6 (t = 0·48, 0·7 > P > 0·6) and offers independent confirmation of it.

The near identity in form of the pre-operative and post-operative relationships for both volume and acid output shows that there is a significant relationship between the spontaneous secretion and the augmented histamine response and that it is not upset by gastrojejunostomy.

## DISCUSSION

The view that gastrojejunostomy has no effect on the actual output of fluid or acid from the stomach is suggested by the number of times the regression coefficient of P has been close to unity in the six correlations obtained between pre-operative and post-operative data. In three of the six correlations there was a difference of less than 5% from unity. Although the differences in the other three were greater, they were not statistically significant. However, gastrojejunostomy does affect the pre-operative data. It does so by a constant amount which varies within limits which can be calculated from the standard deviations. This difference is a constant and is not dependent on the pre-operative volume or acid output as it would be if the actual secretory activity of the cells were involved. Since the only physical change that has taken place in the gastrointestinal tracts of these patients is the making of a gastrojejunostomy stoma, it is not unreasonable to ascribe the volume and acid changes after gastrojejunostomy to the passage of fluid through the stoma in two directions with some neutralization and also some loss. It also seems logical that this traffic through the stoma should be a quantity which is independent of the pre-operative secretory function of the stomach. This thesis is upheld by the correlation equations obtained from the data.

We have already indicated the differences between the constants in equations 1a and 3a, which refer to spontaneous and augmented histamine volumes, and in equations 2a and 5a, which refer to the corresponding acid outputs. This suggests that the traffic through the stoma is altered by giving large doses of histamine. This is not unreasonable and may well be due to alterations in motility and to increases in the production of pancreatic juice and succus entericus.

Hunt and Kay (1954) have already shown that a significant correlation exists between spontaneous secretion and the augmented histamine response but as the time periods of measurement are different no direct comparison between the data can be made. It has, therefore, been interesting to show that the correlation which exists between the spontaneous and the augmented histamine response is maintained after gastrojejunostomy and that the differences due to the operation reside only in the constants and are therefore independent of the actual secretory values. This confirms the general argument outlined above and the actual values of the

constants, particularly in relation to the acid outputs, confirm it more specifically.

The analysis of the data has therefore given us a measure of the effect of the gastrojejunostomy stoma. As far as acid output is concerned, we can say that the gastrojejunostomy reduces the total acid output by approximately 5 mEq. on the average with a standard deviation of about 5. Owing to the large variations in volume the standard deviations are very large and although this has not affected the significance of the correlation equations it is more difficult to predict the post-operative response with accuracy.

These data may prove of value in assessing the effects on acid secretion of any operation on the stomach which involves the formation of a gastrojejunostomy.

## Summary

The effect of gastrojejunostomy on the spontaneous and augmented histamine responses has been studied with reference to the volume and acid outputs in 17 male patients with duodenal ulcer.

Significant correlations were found between the pre-operative and post-operative values for both spontaneous and augmented histamine responses.

Significant correlations were also found between the spontaneous and the augmented histamine responses, pre-operatively and post-operatively.

The regression equations show that gastrojejunostomy has no fundamental effect on the secretory activity of the stomach and that alterations in volume or acid output are entirely due to reflux and/or loss.

Gastrojejunostomy does not affect the relationships between spontaneous secretion and the augmented histamine response.

We wish to express our thanks to Dr. R. A. Robb, of the Mathematics Department, University of Glasgow, for his advice and criticism of the statistical methods employed in this study.

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# A COMPARISON BETWEEN THE EFFECTS OF HEXAMETHONIUM AND ATROPINE IN COMBINATION AND OF VAGOTOMY WITH GASTROJEJUNOSTOMY ON HUMAN GASTRIC SECRETION

BY

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This study records the gastric secretory response, using the Kay augmented histamine test, and compares "medical" vagotomy with atropine and hexamethonium with "surgical" vagotomy. The results suggest that it may be of value in predicting the effect of vagotomy with gastrojejunostomy.

The considerable difference of opinion which exists regarding the surgical treatment of duodenal ulcer suggests that the ideal operation has not yet been devised. The advantages of a lower morbidity rate with vagotomy and gastrojejunostomy compared with partial gastrectomy are offset by the higher incidence of recurrent ulceration in the former procedure (Cox and Kerr, 1957; Everson, Hutchings, Eisen, and Witanowski, 1957). It has been shown that the acid response to the augmented histamine test (Kay, 1953) is greater after vagotomy and gastrojejunostomy than after partial gastrectomy (Gillespie, Clark, Kay, and Tankel, 1960) and it seems possible that this may be responsible for the higher incidence of recurrent ulceration. However, the range of reduction in acid output which could be achieved was wide, and some patients after vagotomy with gastrojejunostomy exhibited acid reductions comparable to those achieved by partial gastrectomy.

It has been shown (Kay and Smith, 1956) that hexamethonium and atropine given in combination will inhibit spontaneous acid gastric secretion and motility through their acetylcholine blocking action. In this investigation we have compared the effect of hexamethonium and atropine with vagotomy and gastrojejunostomy on spontaneous and maximal gastric acid secretion, the latter being estimated by means of the augmented histamine test. It will be shown that significant correlations exist for maximal secretion. This raises the possibility that the effect of hexamethonium and atropine on the augmented histamine response may be of value as a pre-operative test by predicting the reduction in acid-secreting capacity which can be expected to result from vagotomy with gastrojejunostomy in the individual patient with duodenal ulceration.

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## METHOD

Twenty male patients with uncomplicated duodenal ulcer were selected for study. All were subsequently treated by subdiaphragmatic vagotomy with the addition of posterior gastrojejunostomy as the drainage procedure.

An augmented histamine test was carried out on at least two occasions before operation and once or twice after operation between the eighth and twelfth post-operative days.

In one pre-operative test in each patient the augmented histamine test was modified by the prior administration of hexamethonium and atropine in combination so that the acidity of spontaneous acid secretion was reduced to achlorhydria or to near-achlorhydria.

Each test was made after a 12-hour fast. A "neoplex" gastric tube was introduced through the nose and the stomach emptied by means of an electric suction apparatus. Complete aspiration of the gastric juice was achieved by frequently interrupting the suction and injecting a little air to ensure patency of the tube. Care was taken to standardize the tests for each subject by passing the tube to the same distance in each test.

In the augmented histamine tests the fasting juice was first aspirated and discarded. Specimens were then collected at 15-minute intervals for one hour to give one hour's spontaneous secretion. At the end of this period, 100 mg. mepyramine hydrogen maleate ("anthisan") was injected intramuscularly and the gastric juice collected in the subsequent 30 minutes was discarded. Histamine acid phosphate was then injected subcutaneously in a dose

of 0·04 mg./kg. body weight and specimens collected at 15-minute intervals for a further 45 minutes. The last two specimens together were taken to represent the maximal histamine response.

In the modified tests, hexamethonium bromide, 50 mg., with atropine, 0·325 mg., was given as a single intramuscular injection after the fasting gastric juice had been aspirated. Thereafter, 15-minute specimens were taken for 75 minutes. The acid output in the last specimen was taken to represent the effect of the combination of drugs on the spontaneous secretion. Anthisan was now given and the test completed as a standard augmented histamine test.

Each specimen was measured for volume in millilitres, free acid (by titrating against N/10 NaOH with Töpfer's indicator), and the presence or absence of bile was also noted. The output of acid was expressed in milliequivalents HCl per half hour for both spontaneous secretion and the maximal histamine secretion. The percentage change due to hexamethonium and atropine and to vagotomy with gastrojejunostomy was then calculated for each patient. The means of these were calculated both arithmetically and geometrically, since the latter gives a more accurate estimation of the means of percentages than does the arithmetic mean. The regression equations were calculated to four decimal places and then rounded off to two decimal places.

In the following presentation, the use of hexamethonium and atropine will be referred to as "medical" vagotomy and that of vagotomy with gastrojejunostomy as "surgical" vagotomy.

## Results

Maximal Histamine Response: Acid Output.—The acid outputs in response to the augmented histamine test before and after "medical" and "surgical" vagotomy are shown in Table I. A reduction was effected in all cases after hexamethonium and atropine; the mean reduction was 37·3%, which is statistically significant at the 1% level. Vagotomy with gastrojejunostomy likewise produced a reduction in the augmented histamine response in all cases, the mean reduction being 59·1% which is also statistically significant at the 1% level. This reduction was generally greater than that following hexamethonium and atropine and the difference between the two is also significant statistically. It will be noted that in patients Nos. 8, 9, and 19 the response to surgery was less than that due to "medical" vagotomy.

The volume outputs (Table II) after "medical" vagotomy show a mean reduction of 34·6% which is of the same order as the reduction in acid output (mean 37·3%). However, the reduction in volume after operation (32·8%) is proportionately very much less than the reduction in acid output (59·1%). This picture of a larger than expected volume after operation may be explained by reflux of bile and duodenal juice through the gastrojejunostomy stoma. However, more information can be obtained by examining the correlations between the sets of data.

Fig. 1 shows the acid outputs in response to the augmented histamine test after "medical" vagotomy (M) plotted against the simple augmented histamine outputs (P). There is a significant correlation between the two sets of data ($r = 0{\cdot}7930$, $P<0{\cdot}01$) and the regression of P on M is given by

$M = 0{\cdot}44P + 3{\cdot}10$ (equation 1) (standard error of the estimate $= \pm 1{\cdot}89$).

TABLE I

EFFECT OF "MEDICAL" AND "SURGICAL" VAGOTOMY ON AUGMENTED HISTAMINE RESPONSE*

| Patient No. | Before Vagotomy (P) | After "Medical" Vagotomy (M) | % Reduction | After "Surgical" Vagotomy (S) | % Reduction |
|---|---|---|---|---|---|
| 1 | 23·6 | 13·6 | 42·4 | 6·3 | 73·3 |
| 2 | 17·8 | 10·5 | 41·0 | 6·5 | 63·5 |
| 3 | 18·1 | 11·0 | 39·2 | 6·4 | 64·6 |
| 4 | 21·6 | 14·4 | 33·3 | 4·5 | 79·2 |
| 5 | 16·1 | 8·5 | 47·2 | 5·0 | 68·9 |
| 6 | 10·6 | 7·5 | 29·2 | 5·3 | 50·0 |
| 7 | 17·3 | 14·5 | 16·2 | 11·8 | 31·8 |
| 8 | 16·1 | 8·9 | 44·7 | 9·1 | 43·5 |
| 9 | 28·6 | 15·7 | 45·1 | 17·7 | 38·1 |
| 10 | 30·7 | 13·5 | 56·0 | 6·8 | 77·9 |
| 11 | 14·0 | 7·6 | 45·7 | 2·0 | 85·7 |
| 12 | 21·9 | 13·4 | 38·8 | 8·1 | 63·0 |
| 13 | 23·0 | 13·5 | 41·3 | 7·7 | 66·5 |
| 14 | 16·6 | 11·3 | 31·9 | 0·0 | 100·0 |
| 15 | 21·9 | 16·5 | 24·7 | 9·9 | 54·8 |
| 16 | 13·1 | 9·1 | 30·5 | 7·2 | 45·0 |
| 17 | 18·7 | 13·1 | 30·0 | 7·6 | 59·4 |
| 18 | 12·2 | 5·5 | 54·9 | 1·3 | 89·3 |
| 19 | 17·6 | 11·6 | 34·1 | 12·1 | 31·2 |
| 20 | 26·5 | 13·6 | 48·7 | 11·8 | 55·5 |
| Arithmetic mean | 19·30 | 11·67 | 38·7 | 7·36 | 62·1 |
| Geometric mean | — | — | 37·3 | — | 59·1 |
| ± S.D. | 5·56 | 3·10 | — | 4·21 | — |

* Acid output is expressed in mEq./half hour.

TABLE II
EFFECT OF "MEDICAL" AND "SURGICAL" VAGOTOMY ON AUGMENTED HISTAMINE RESPONSE*

| Patient No. | Before Vagotomy (P) | After "Medical" Vagotomy (M) | % Reduction | After "Surgical" Vagotomy (S) | % Reduction |
|---|---|---|---|---|---|
| 1 | 195 | 113 | 42·0 | 97 | 50·3 |
| 2 | 144 | 98 | 31·9 | 77 | 46·5 |
| 3 | 142 | 99 | 30·3 | 131 | 7·7 |
| 4 | 171 | 126 | 26·3 | 78 | 54·4 |
| 5 | 148 | 80 | 45·9 | 62 | 58·1 |
| 6 | 113 | 73 | 35·4 | 48 | 57·5 |
| 7 | 144 | 134 | 6·9 | 123 | 14·6 |
| 8 | 147 | 75 | 49·0 | 107 | 27·2 |
| 9 | 228 | 124 | 45·6 | 160 | 29·8 |
| 10 | 236 | 133 | 43·6 | 138 | 41·5 |
| 11 | 123 | 68 | 44·7 | 66 | 46·3 |
| 12 | 184 | 116 | 37·0 | 104 | 43·5 |
| 13 | 186 | 117 | 37·1 | 124 | 33·3 |
| 14 | 166 | 92 | 44·6 | 59 | 64·5 |
| 15 | 205 | 151 | 26·3 | 114 | 44·4 |
| 16 | 124 | 98 | 21·0 | 95 | 23·4 |
| 17 | 163 | 99 | 39·3 | 152 | 6·7 |
| 18 | 139 | 59 | 57·6 | 57 | 59·0 |
| 19 | 147 | 103 | 29·9 | 125 | 15·0 |
| 20 | 225 | 112 | 50·2 | 119 | 47·1 |
| Arithmetic mean | 166·5 | 103·5 | 37·2 | 101·8 | 38·5 |
| Geometric mean | — | — | 34·6 | — | 32·8 |
| ± S.D. | 37·3 | 25·0 | — | 34·1 | — |

* Volume is expressed in ml./half hour.

Similarly Fig. 1 also shows the post-operative outputs (S) plotted against the pre-operative outputs (P). The correlation is again significant ($r = 0{\cdot}5195$; $0{\cdot}02 > P > 0{\cdot}01$) and the regression of S on P is given by

$S = 0{\cdot}40P - 0{\cdot}29$ (equation 2) (standard error of the estimate $\pm$ 3·60).

It is obvious by inspection of the equations that the two relationships are similar and that the difference between them is almost constant as is indicated by the fact that the lines on the graph are almost parallel. The regression coefficients 0·44 and 0·40 are not significantly different from each other ($t = 0{\cdot}50$; $0{\cdot}7 > P > 0{\cdot}6$) and suggest that "medical" vagotomy reduces the output by 56% while surgery reduces the output by 60% and that the difference between "medical" and "surgical" vagotomy resides mainly in the constants which are significantly different from each other ($t = 8{\cdot}04$; $P < 0{\cdot}01$).

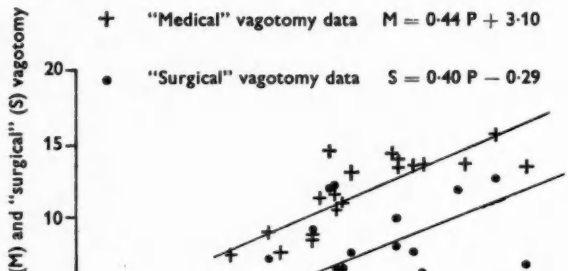


FIG. 1.—*The correlations of the pre-operative data with "medical" vagotomy and with "surgical" vagotomy are shown (acid outputs in mEq./half hour). The similarity between the two relationships can be clearly seen, the lines being almost parallel so that the differences at any point are almost constant.*

When the actual individual differences between M and S, *i.e.*, the differences between "medical" and "surgical" vagotomy, are plotted against the corresponding values of P the regression equation is found to be

$$M - S = 4{\cdot}31 + 0{\cdot}04\,(P - 19{\cdot}3)$$

and since 0·04 is a very small factor of P and is not significantly different from zero, the equation may be reduced to

$$M - S = 4{\cdot}31 \text{ (equation 3)}$$

The same answer is obtained by subtracting equation 2 from equation 1 when allowance is made for rounding.

Thus by each of these methods the difference between "medical" (M) and "surgical" (S) vagotomy is shown to be a constant independent of P, the initial secretory activity of the stomach, and with a mean value of 4.31.

Can the differences between "medical" vagotomy and "surgical" vagotomy be explained purely on the basis of the gastro-jejunostomy stoma?

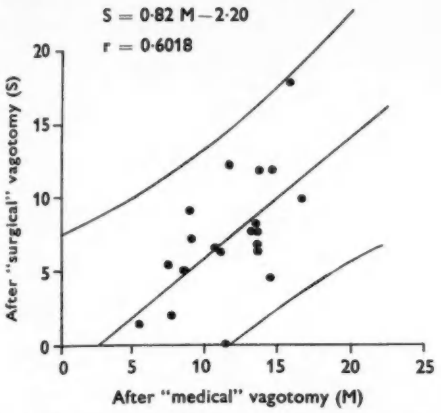


FIG. 2.—*The relationship between the acid output responses to "medical" and "surgical" vagotomy with the corresponding 95% confidence limits.*

In a previous paper (Tankel, Gillespie, Clark, Kay, and McArthur, 1960) we have shown that there is a significant correlation between the pre-operative acid outputs (P) and the outputs after simple gastrojejunostomy (G).

The relationship is given by the regression equation

$$G = 1{\cdot}03P - 5{\cdot}53$$

which was reduced to

$$G - P = 4{\cdot}94^{*} \text{ (equation 4)}$$

and it was argued that the constant 4·94 was the mean loss in output due to a combination of neutralization by the passage of intestinal juice into the stomach and loss across the stoma, and was independent of the initial secretory activity of the stomach. If the difference between "medical" vagotomy and "surgical" vagotomy is the same as the difference between pre- and post-gastrojejunostomy then it would suggest that the difference between "medical" and "surgical" vagotomy is due solely to the presence of a gastrojejunostomy stoma. In fact, this is so, and the constant 4·31 is not significantly different from the constant 4·94 ($t = 0{\cdot}65$; $0{\cdot}6 > P > 0{\cdot}5$). Therefore, the difference between the responses to the augmented histamine test after "medical" vagotomy and after "surgical" are probably due solely to the effects of the gastrojejunostomy. However, this point can be approached more directly.

Fig. 2 shows the outputs after "medical" vagotomy (M) plotted directly against the outputs after gastrojejunostomy with vagotomy (S). There is a significant correlation ($r = 0{\cdot}6018$; $P < 0{\cdot}01$) and the regression of M on S is given

$S = 0{\cdot}82M - 2{\cdot}20$ (equation 5) (standard error of the estimate $= \pm 3{\cdot}37$).

The factor 0·82 is not significantly different from 1·00 ($t = 0{\cdot}58$; $0{\cdot}6 > P > 0{\cdot}5$) and the equation can thus be reduced to

$$S = M - 4{\cdot}31$$

since the mean value of $M = 11{\cdot}67$

or $M - S = 4{\cdot}31$ (equation 6)

which is identical with equation 3 and helps to confirm the argument already outlined.

MAXIMAL HISTAMINE RESPONSE: VOLUME.—Fig. 3 shows the volumes after "medical" vagotomy (M) plotted against the volumes of the pre-operative augmented histamine response (P). There is a significant correlation ($r = 0{\cdot}7048$; $P < 0{\cdot}01$) between the two sets of data and the regression of P on M is given by

$M = 0{\cdot}47P + 24{\cdot}90$ (equation 7) (standard error of the estimate $= \pm 17{\cdot}73$).

Similarly Fig. 3 shows the volumes after "surgical" vagotomy (S) plotted against the pre-operative volumes (P). There is again a significant correlation ($r = 0{\cdot}5745$; $P < 0{\cdot}01$) and the regression of P on S is given by

$S = 0{\cdot}52P + 14{\cdot}54$ (equation 8) (standard error of the estimate $= \pm 27{\cdot}88$).

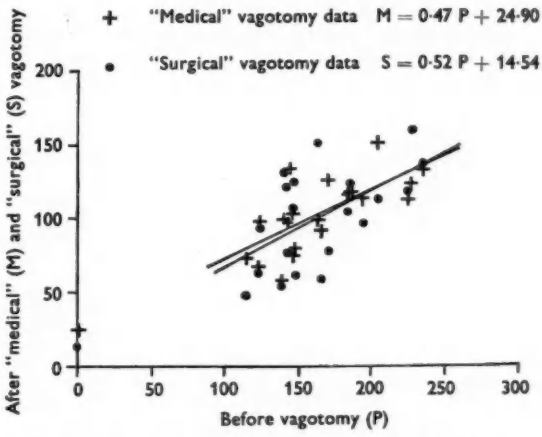


FIG. 3.—*The correlations of the pre-operative data with "medical" vagotomy and with "surgical" vagotomy are shown (volumes in ml./half hour). There is a similarity between the two relationships and the lines are almost superimposed.*

*This is obtained as follows:—

$G = 1{\cdot}0345P - 5{\cdot}5289$

$= P + 0{\cdot}0345 \times 17{\cdot}0035 - 5{\cdot}5289$

(Since the mean value of $P = 17{\cdot}0035$)

$= P + 0{\cdot}5866 - 5{\cdot}5289$

$= P + 4{\cdot}9423.$

Once again there is an obvious similarity between the two equations and, on the graph, the lines are almost superimposed. The regression coefficients 0·47 and 0·52 are not significantly different from each other ($t = 0{\cdot}44$; $0{\cdot}7 > P > 0{\cdot}6$) and suggest that "medical" vagotomy causes a reduction of 53% and "surgical" vagotomy produces a reduction of 48% in the pre-operative volumes, with a further constant reduction of about 10 ml.

Again we may calculate the actual individual differences (M − S) and may compare them directly with the corresponding pre-operative volume (P). The regression of (M − S) on P is given by

$$M - S = 1{\cdot}70 - 0{\cdot}6\,(P - 166{\cdot}5)$$

Since 0·06 is not significantly different from zero this becomes

$$M - S = 1{\cdot}70 \text{ (equation 9)}$$

This may also be obtained by subtracting equation 8 from equation 7. In our previous paper (Tankel *et al.*, 1960) we have already shown that in the response to the augmented histamine test there is a significant correlation between pre-operative volume (P) and the volume after gastrojejunostomy (G), the relationship being given by the equation

$$G = 1{\cdot}23P - 39{\cdot}21$$

which was reduced to

$$P - G = 3{\cdot}47 \text{ (equation 10)}$$

and there is no significant difference between the constants 3·47 and 1·70 ($t = 0{\cdot}23$; $0{\cdot}9 > P > 0{\cdot}8$). This suggests that gastrojejunostomy explains the difference between "medical" and "surgical" vagotomy as far as volume is concerned.

This point can also be approached more directly. Fig. 4 shows the volumes after "surgical" vagotomy (S) plotted against the volumes following "medical" vagotomy (M). The correlation is significant ($r = 0{\cdot}6113$; $P < 0{\cdot}01$) and the regression equation of M on S is given by

$$S = 0{\cdot}83\,M + 15{\cdot}63 \text{ (equation 11) (standard error of the estimate} = \pm 26{\cdot}95).$$

The correlation coefficient of 0·83 for volume is almost identical with the correlation coefficient of 0·82 for acid output, and, like it, is not significantly different from 1·00 ($t = 0{\cdot}55$; $0{\cdot}6 > P > 0{\cdot}5$). Proceeding on this assumption, therefore, the formula may be reduced to

$$S = M - 1{\cdot}70$$

or

$$M - S = 1{\cdot}70 \text{ (equation 12)}$$

which is identical with equation 9 which has already been deduced by a different method.

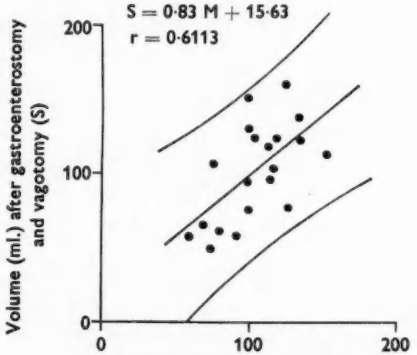


FIG. 4.—*The relationship between the volume responses to "medical" and "surgical" vagotomy with the corresponding 95% confidence limits.*

SPONTANEOUS SECRETION.—Hexamethonium and atropine effect a gradual reduction in spontaneous secretion during the subsequent hour; achlorhydria resulted in 12 patients, and near achlorhydria in the remaining eight patients in the final 15-minute period (Table III). The final 15-minute period has, therefore, been taken to represent the effect of "medical" vagotomy on the spontaneous secretory rate. The mean reduction in the acid output is 98·7%.

Following "surgical" vagotomy there was also a considerable and invariable reduction in the spontaneous acid output (mean 78·3%) but in only seven patients did achlorhydria result, and in only two other patients was the level found to be as low as that produced after "medical" vagotomy. "Medical" vagotomy, therefore, produced a more profound reduction in the spontaneous acid gastric output than did "surgical" vagotomy, and this difference is statistically significant ($P < 0{\cdot}01$).

When the volumes are considered (Table IV), there is an invariable drop in secretion following "medical" vagotomy but the volume was increased in 11 of the 20 patients after "surgical" vagotomy so that the mean difference was only 4·3%. Since there is still a big reduction in acid output, the failure of "surgical" vagotomy to reduce the volume may be due to the reflux of bile and duodenal juice into the stomach. This is borne out by the fact that bile was present in the post-operative specimens of spontaneous secretion in 18 out of 20 patients.

The correlations between the pre-operative data (P) and the "surgical" vagotomy data (S) on the one hand and between the pre-operative data (P) and the "medical" vagotomy data (M) on the other hand for both volume and acid output were not significant. This was due to the fact that volumes and acid outputs were reduced to such low levels after both "medical" and "surgical" vagotomy that measurement was difficult and the associated error high.

TABLE III

EFFECT OF "MEDICAL" AND "SURGICAL" VAGOTOMY ON SPONTANEOUS SECRETION*

| Patient No. | Before Vagotomy (P) | After† "Medical" Vagotomy (M) | % Reduction | After "Surgical" Vagotomy (S) | % Reduction |
|---|---|---|---|---|---|
| 1 | 5·60 | 0·00 | 100·0 | 0·19 | 96·6 |
| 2 | 1·88 | 0·02 | 98·9 | 1·27 | 32·4 |
| 3 | 0·72 | 0·00 | 100·0 | 0·00 | 100·0 |
| 4 | 3·13 | 0·17 | 94·6 | 0·39 | 87·5 |
| 5 | 1·56 | 0·00 | 100·0 | 0·13 | 91·7 |
| 6 | 0·94 | 0·00 | 100·0 | 0·00 | 100·0 |
| 7 | 1·76 | 0·00 | 100·0 | 1·31 | 25·6 |
| 8 | 1·61 | 0·00 | 100·0 | 0·92 | 42·9 |
| 9 | 1·85 | 0·00 | 100·0 | 0·53 | 71·4 |
| 10 | 4·82 | 0·00 | 100·0 | 0·48 | 90·0 |
| 11 | 2·36 | 0·00 | 100·0 | 0·00 | 100·0 |
| 12 | 3·45 | 0·05 | 98·6 | 0·01 | 99·7 |
| 13 | 3·88 | 0·00 | 100·0 | 0·81 | 79·1 |
| 14 | 2·73 | 0·13 | 95·2 | 0·00 | 100·0 |
| 15 | 3·67 | 0·24 | 93·5 | 0·93 | 74·7 |
| 16 | 4·73 | 0·09 | 98·1 | 0·00 | 100·0 |
| 17 | 4·58 | 0·16 | 96·5 | 0·92 | 79·9 |
| 18 | 0·69 | 0·00 | 100·0 | 0·00 | 100·0 |
| 19 | 2·82 | 0·03 | 98·9 | 0·00 | 100·0 |
| 20 | 4·70 | 0·00 | 100·0 | 0·43 | 90·9 |
| Arithmetic mean | 2·874 | 0·044 | 98·7 | 0·42 | 83·1 |
| Geometric mean | — | — | 98·7 | — | 78·3 |
| ± S.D. | 1·54 | 0·075 | — | 0·47 | — |

* Acid output is expressed in mEq./half hour.
† Estimated on the secreting rate one hour after the injections of hexamethonium and atropine.

TABLE IV

EFFECT OF "MEDICAL" AND "SURGICAL" VAGOTOMY ON SPONTANEOUS SECRETION*

| Patient No. | Before Vagotomy (P) | After† "Medical" Vagotomy (M) | % Reduction | After "Surgical" Vagotomy (S) | % Change |
|---|---|---|---|---|---|
| 1 | 69·5 | 3·0 | 95·7 | 52·5 | − 24·5 |
| 2 | 35·5 | 2·0 | 94·4 | 40·5 | + 14·1 |
| 3 | 29·0 | 1·0 | 96·6 | 83·0 | +186·2 |
| 4 | 67·5 | 14·0 | 79·3 | 36·0 | − 46·7 |
| 5 | 37·5 | 1·0 | 97·3 | 39·0 | + 4·0 |
| 6 | 30·0 | 4·0 | 86·7 | 35·5 | + 18·3 |
| 7 | 58·0 | 1·0 | 98·3 | 46·5 | − 19·8 |
| 8 | 48·5 | 4·0 | 91·8 | 68·5 | + 41·2 |
| 9 | 36·0 | 6·0 | 83·3 | 49·5 | + 37·5 |
| 10 | 83·5 | 2·0 | 97·6 | 81·5 | − 2·4 |
| 11 | 52·0 | 1·0 | 98·1 | 22·0 | − 57·7 |
| 12 | 58·5 | 2·0 | 96·6 | 21·5 | − 63·2 |
| 13 | 53·5 | 12·0 | 77·6 | 58·0 | + 8·4 |
| 14 | 48·0 | 4·0 | 91·7 | 62·5 | + 30·2 |
| 15 | 73·5 | 20·0 | 72·8 | 77·0 | + 4·8 |
| 16 | 58·5 | 4·0 | 93·2 | 57·5 | − 1·7 |
| 17 | 73·5 | 5·0 | 93·2 | 76·0 | + 3·4 |
| 18 | 39·5 | 2·0 | 94·9 | 66·5 | + 68·4 |
| 19 | 58·5 | 2·0 | 96·6 | 21·5 | − 63·2 |
| 20 | 74·0 | 2·0 | 97·3 | 36·0 | − 51·4 |
| Arithmetic mean | 54·2 | 4·6 | 91·7 | 51·6 | + 4·3 |
| Geometric mean | — | — | 91·3 | — | — |
| ± S.D. | 16·58 | 5·16 | — | 20·51 | — |

* Volume is expressed in ml./half hour.
† Estimated on the secreting rate one hour after the injection of hexamethonium and atropine.

## DISCUSSION

Both "medical" vagotomy and "surgical" vagotomy have a profound inhibitory effect on the volume and the acid output of spontaneous secretion and the augmented histamine response.

As regards spontaneous secretion, this profound inhibition, which resulted in complete achlorhydria or near achlorhydria in all of the 20 patients after "medical" vagotomy and in nine patients after "surgical" vagotomy, was significant but precluded the demonstration of correlations.

However, significant correlations were obtained between the groups of responses to the augmented histamine test. It has already been argued from regression equations 1 and 2 that "surgical" vagotomy produces a reduction of 60% in acidity and "medical" vagotomy a reduction of 56%, and that the differences between these percentages is not

significant. We have also shown that the difference between "medical" and "surgical" vagotomy tends to be a constant, independent of gastric secretory activity and, in this study, was found to be 4·31 mEq. This value is not significantly different from the constant 4·94 mEq. previously calculated by us as being the effect of a simple gastrojejunostomy (Tankel *et al.*, 1960). It has, therefore, been argued that the difference between "medical" and "surgical" vagotomy was due solely to the constant reduction produced by the gastrojejunostomy. Thus, the use of regression equations has enabled us to estimate the true reduction due to "surgical" vagotomy by allowing for the effect of the stoma.

Similarly we have shown from equations 7 and 8 that "surgical" vagotomy reduces the volume by 48% and "medical" vagotomy reduces it by 53%, the difference between them once again being constant and independent of the secretory activity of the stomach.

This study was undertaken in order to compare the effect of "medical" vagotomy and of "surgical" vagotomy on the acid output and volume of the gastric secretion (Figs. 2 and 4). The 95% confidence limits are wide because of the degree of variations from individual to individual. However, the degree of correlation between the "medical" and "surgical" data raises the possibility that the effect of "medical" vagotomy on the augmented histamine response may be of value in predicting the effect of "surgical" vagotomy.


## Summary

A comparison has been made between the effect of hexamethonium and atropine and vagotomy with gastrojejunostomy on the volume and acid output of human gastric secretion. Significant correlations exist in response to the augmented histamine test though not for spontaneous secretion. This raises the possibility that the effect of hexamethonium and atropine on the augmented histamine response may be of value in predicting the effect of vagotomy with gastrojejunostomy.


We wish to express our thanks to Dr. R. A. Robb of the Mathematics Department, University of Glasgow, for his advice and criticism of the statistical methods employed in this study.

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# MASSIVE RESECTION OF THE SMALL INTESTINE AFTER OCCLUSION OF THE SUPERIOR MESENTERIC ARTERY

BY

R. J. HARRISON and C. C. BOOTH

*From St. James's Hospital, Balham, London, and the Postgraduate Medical School of London*

Resection of all the small intestine but the proximal 8 in. of jejunum was performed in an elderly woman. Intestinal function tests revealed an extensive defect of absorption. The patient died nine months after the operation in a state of extreme emaciation. Necropsy revealed hypertrophy of the remnant of small intestine and intense fatty degeneration of the liver.

Occlusion of the superior mesenteric artery is one of the commoner causes of extensive gangrene of the small intestine (Haymond, 1935). Resection of large amounts of the small bowel may be necessary but this procedure carries a high post-operative mortality (Bowen and Felger, 1942). Uricchio, Calenda, and Freedman (1954) estimated that approximately 1,350 cases of mesenteric artery occlusion had been reported in the literature but they were able to find only 158 cases in which recovery followed resection. Thirty-two patients were studied by Wilson and Block (1956); 12 were subjected to resection and only two of these survived for as long as three months. In individual cases, however, extensive resection after arterial obstruction may be compatible with life and survival is possible with only 14 to 18 in. of residual small intestine (Meyer, 1946 and 1954; Cogswell, 1948; Althausen, Uyeyama, and Simpson, 1949; Schwartze, Medwid, Roberts, Sleisenger, and Randall, 1956; Kogan, Schapira, Janowitz, and Aldersberg, 1957).

We have recently had the opportunity of observing a woman who had an extensive resection of the small intestine after thrombosis of the superior mesenteric artery. Only 8 in. of the jejunum remained, yet she survived for nine months after the operation.

## Case Report

A.S., a widow aged 80, was admitted to St. James's Hospital, Balham, on November 20, 1958, complaining of progressive shortness of breath on exertion and epigastric discomfort after meals.

Clinical examination showed a healthy-looking elderly woman (weight 9 st. 4 lb.). The mucous membranes were pale. Jugular venous pressure was elevated to 2 cm. above the sternal angle, slight sacral oedema was noted, and fine crepitations were heard over both lung bases. The pulse was regular and blood pressure 225/115 mm. Hg. The apex beat was palpable in the fifth left intercostal space $\frac{1}{2}$ in. outside the midclavicular line. A soft systolic murmur was present in the aortic area.

Investigations revealed Hb 6·1 g. % (48%); R.B.C.s 3·1 m. per c.mm.; P.C.V. 25%; and W.B.C. 7,950 per c.mm. Stained blood films showed evidence of iron deficiency. Occult blood was present in the stools. Serum proteins were 6·5 g. % (albumin 4·4 g., globulin 2·1 g.) and blood urea 32 mg. %. A radiograph of the chest showed slight left ventricular enlargement and a barium meal revealed a small sliding hiatus hernia. In the E.C.G. there was inversion of the T waves over the anterior chest leads (V3 to 6), suggesting left ventricular ischaemia.

Treatment and Progress.—A diagnosis of iron-deficiency anaemia secondary to chronic blood loss from a hiatus hernia was made. She was treated with oral iron (ferrous sulphate, grains 3, three times daily). She also received "digoxin" (0.25 mg. three times daily) and chlorothiazide (1 g. once weekly). On November 26 (one week after admission) she had an acute attack of pain in the left lower chest, radiating to the left shoulder and exaggerated by inspiration. She was not shocked (B.P. 215/105) but an E.C.G. now showed further inversion of the T waves, suggesting an episode of myocardial ischaemia. The pain was relieved by pethidine (100 mg. subcutaneously) and did not recur. By December 13, the Hb had risen to 68% and she felt well. On December 20 she was discharged home, but that night she had an attack of abdominal pain and vomiting. She recovered from this but on December 25 before breakfast she had a sudden attack of severe abdominal pain followed by vomiting, and was readmitted to St. James's Hospital, Balham, at once.

Clinical examination revealed generalized abdominal tenderness and guarding, and the bowel sounds were absent. Her pulse was regular; blood pressure was

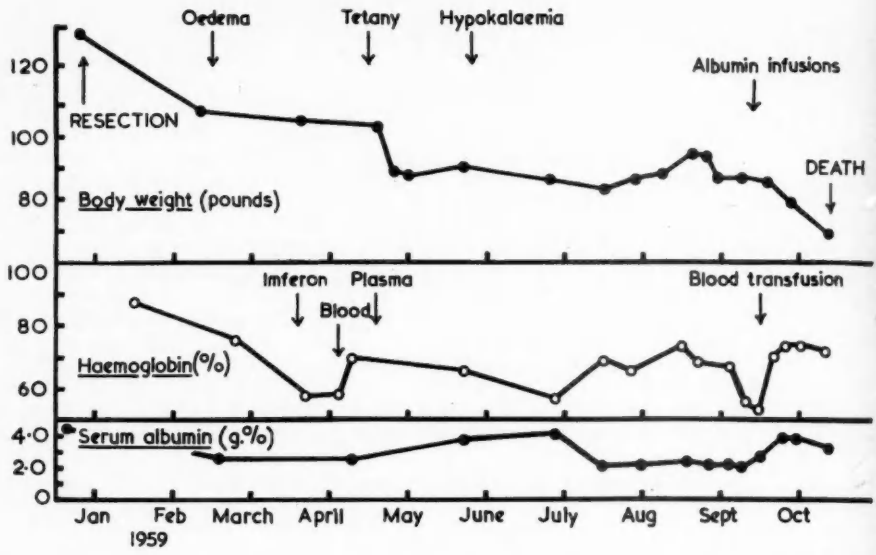


FIG. 1.—*Body weight, haemoglobin, and serum albumin levels from the time of the resection until death.*

130/90 mm. Hg and the jugular venous pressure not raised.

TREATMENT AND PROGRESS AFTER READMISSION.—A diagnosis of peritonitis was made and immediate laparotomy was performed (Mr. I. Penn). There was foul-smelling purulent fluid in the peritoneal cavity and the intestine was found to be gangrenous from a point just beyond the duodeno-jejunal flexure to the mid-ascending colon. The superior mesenteric artery was not pulsating and was occluded by thrombus. As a life-saving measure an extensive resection was carried out, an end-to-end anastomosis being performed between the upper jejunum and the ascending colon. It was estimated that approximately 8 in. of jejunum remained. Post-operatively the patient was treated with parenteral fluids and antibiotics. She made a good recovery and by December 31 was able to take a light fluid diet, although she had profuse diarrhoea, passing between two and 12 loose, watery motions daily. She was treated with a high-protein, low-fat diet (approximately 30 g. fat daily) and she also received parenteral injections of vitamins A, $B_{12}$, $D_1$ and K. Her subsequent progress is illustrated in Fig. 1. Seven weeks after the operation her weight had decreased by 22 lb. and the serum albumin had fallen to 2·7 g. %; ankle oedema developed. Her protein intake was increased to approximately 100 g. daily. Twelve weeks post-operatively she had persistent oedema; haemoglobin had fallen to 56%, although there was no occult blood in the stools. Chlorothiazide (1 g. twice weekly) was started and she was given "imferon" (40 ml. in divided doses during the next two weeks). The haemoglobin did not rise and 2 pints of blood were then given. By the middle of April, 1959 (16 weeks post-operatively), she had developed tetany (serum Ca 4·3 mEq./litre) which was relieved by injections of calcium gluconate. The oedema and hypoproteinaemia persisted and 5 pints of plasma were given by intravenous infusion. The serum albumin level increased following this treatment and there was a diuresis with further loss of weight (Fig. 1). At this time she was feeling well and she was able to take a high-protein, low-fat diet that included beef steak, sole, and chicken. She now passed between one and three bulky, fluid stools daily. In May, 1959, following a bout of severe diarrhoea, the serum potassium level fell to 2·6 mEq./litre and she was given oral potassium chloride (1 g. three times daily). She was also treated with testosterone propionate (5 mg. daily) and liver extract (1 ml. of "hepostab" weekly). On July 16, 1959, she was transferred to Hammersmith Hospital.

Clinical examination showed her to be a bright, alert old lady with signs of marked wasting and weight loss. Blood pressure was 140/90 mm. Hg. There was moderate oedema of the legs and sacrum, but the jugular venous pressure was not elevated.

INVESTIGATIONS OF INTESTINAL FUNCTION.—The following investigations were performed:—

*Intestinal Anatomy.*—A barium follow-through showed slight dilatation of the small amount of remaining small intestine (Fig. 2). Some of the barium had passed into the colon within five minutes.

FIG. 2.—*Barium follow-through examination (10-minute film) showing stomach, remaining small intestine, and ascending colon.*

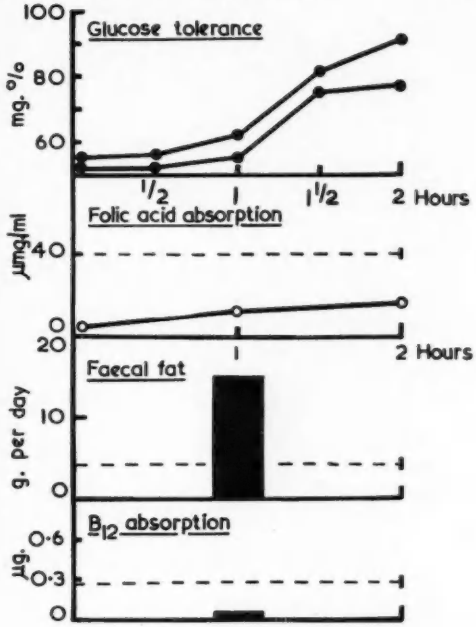


FIG. 3.—*Intestinal function tests. After an oral dose the serum level of folic acid is greater than 40 µg. per ml. in control subjects (Chanarin* et al., *1958). Normal $B_{12}$ absorption from an oral dose of 1 µg. is greater than 0·28 µg. (Mollin* et al., *1957).*

*Intestinal Function Tests.*—These are shown in Fig. 3. Glucose tolerance tests were flat and slow to rise. Folic acid absorption was subnormal (Chanarin, Anderson, and Mollin, 1958). While on a 30 g. fat diet, her faecal fat excretion was 15 g. per day over a three-day balance period. Her absorption of $^{58}$Co-labelled $B_{12}$ was measured using the method described by Glass (1954) and showed no absorption of this vitamin.

*Haematological Findings.*—Haemoplasm was 9·7 g.% (59%), R.B.C.s 3·3 m. per c.mm., P.C.V. 28%. Sternal marrow showed normoblastic erythropoiesis with abundant iron stores. Serum $B_{12}$ concentration was 310 µµg. per ml. (normal 140 to 900 µµg. per ml., Mollin and Ross, 1957). No occult blood was found in specimens of faeces tested repeatedly.

*Proteins and Electrolytes.*—Serum proteins were 4·4 g. per 100 ml. (albumin 2·0 g., globulin 2·4 g.). Serum Na was 145, K 3·6, Cl 104, and $HCO_3$ 27 mEq./litre. Serum Ca was 4·0 and phosphate 1·2 mEq./litre. Alkaline phosphatase was 10 King-Armstrong units.

TREATMENT AND PROGRESS.—At this time the patient was passing between one and three fluid stools daily, A diet containing 40 g. of fat produced severe diarrhoea. as did a fluid diet consisting of glucose drinks and fruit juice; diarrhoea was best controlled by a solid high-protein diet containing less than 30 g. of fat daily. Despite this treatment, serum albumin remained low and anaemia persisted. Her weight increased gradually as she accumulated oedema (Fig. 1) but fell when "mersalyl" (2 ml. once weekly) was given. By the middle of September, 1959, Hb had fallen to 54% but sternal marrow examination again showed normoblastic erythropoiesis and no occult blood was present in the stools. She was given 2 pints of blood and intravenous infusions of salt-free human albumin (total 450 g.) and haemoglobin and serum proteins increased (Fig. 1). Her general condition, however, deteriorated steadily and by September 29, 1959, she had developed signs of a right basal pneumonia. Serum magnesium was measured at this time and was found to be 1·5 mEq./litre (normal 1·5 to 1·8 mEq./litre). She died in a condition of extreme emaciation on October 8.

NECROPSY FINDINGS (Professor C. V. Harrison).—The necropsy confirmed the extremely emaciated appearance of the patient. Internally, the remaining jejunum measured 25 cm.; it was soundly anastomosed to the mid-ascending colon. After fixation the jejunum measured 19 cm. in length and had a circumference of between 11 and 13 cm. (Fig. 4). A similar length of

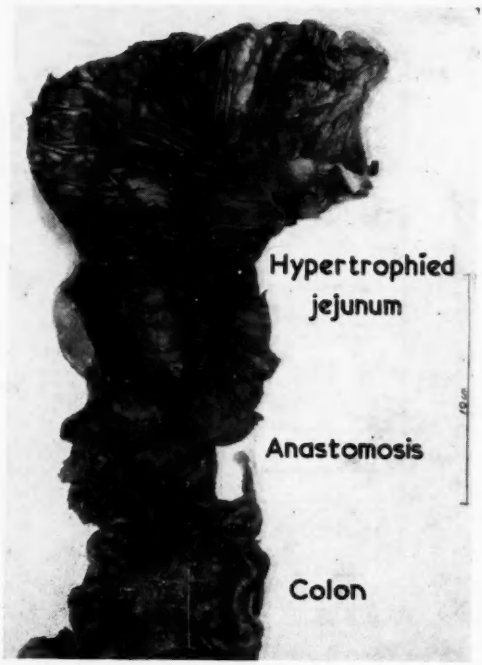


FIG. 4.—*Necropsy specimen of jejunum showing marked enlargement in transverse diameter due to hypertrophy of mucosal and muscle layers.*

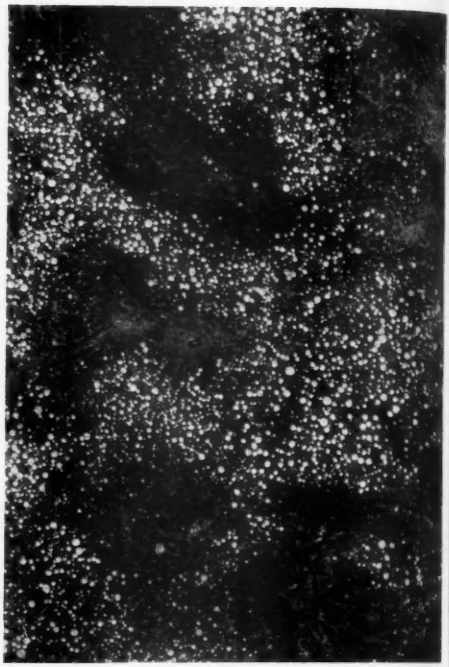

FIG. 5.—*Photomicrograph of liver (×36) showing intense fatty degeneration (haemotoxylin and eosin).*

jejunum from a woman aged 65 had a circumference of 6·5 to 7·5 cm. The weights of the remaining jejunum and of the control specimen were 90 g. and 72 g. respectively. Microscopically, the muscle wall of the jejunum appeared hypertrophied and the mucosa showed many mitoses. The colon appeared normal.

The liver weighed 1,015 g. and showed marked fatty change, mainly in the periportal areas (Fig. 5). The pancreas was normal.

The pericardium was totally adherent and showed small plaques of calcification and of old caseation. Microscopically these were fibrous and acellular but there were also some recent tubercles. The heart was of normal size. The aorta showed mild atheroma.

The right pleura was loosely adherent and the visceral layer showed a series of raised plaques which proved to be tubercles. The right lung was oedematous and there was a purulent bronchitis. Microscopically there was early pneumonia and in some alveoli the reaction was tuberculous. A single acid-fast bacillus was seen in one of these lesions. The left lung showed a basal infarct.

## DISCUSSION

The cause of the mesenteric vascular occlusion in this patient was uncertain. Since there was no obvious source of embolism, it seems likely that it was due to thrombosis of the superior mesenteric artery. Thrombosis may sometimes occur during the course of treatment of chronic anaemia and this may have happened in our patient.

Estimations of the amount of small intestine remaining after massive resection are notoriously inaccurate (Flint, 1912). In this patient, however, the surgeon's observation that 8 in. of jejunum remained was confirmed by the radiological studies (Fig. 2) and at necropsy (Fig. 4). It is therefore not surprising that barium passed through the remaining small intestine within five minutes or that there was an extensive defect in intestinal absorption (Fig. 3). The glucose tolerance curves were flat and rose slowly, suggesting that glucose may have been absorbed from the colon rather than the small intestine in this patient (Jackson, 1958). Folic acid absorption was subnormal, indicating that this substance requires more than 8 in. of the jejunum for its absorption. Although there was marked steatorrhoea, it appeared that approximately 50% of the dietary fat (30 g.) was absorbed from the

small amount of residual intestine. Absorption of $B_{12}$ has been found to be subnormal in patients subjected to massive intestinal resection (McIntyre, Sachs, Krevans, and Conley, 1956; Mollin, Booth, and Baker, 1957). This is in keeping with the observation that $B_{12}$ is absorbed in the ileum in man (Booth and Mollin, 1959). It was not possible to obtain satisfactory data for nitrogen balance studies in this patient. However, the progressive loss of weight, hypoalbuminaemia, and oedema indicate that she was unable to absorb sufficient protein to maintain nutrition. It is in fact surprising that she survived for as long as nine months.

The cause of the persistent anaemia is uncertain. There was no evidence of any specific vitamin deficiency. She had been given injections of vitamin $B_{12}$ and the serum $B_{12}$ concentration was normal. Sternal marrow on two occasions revealed no evidence of megaloblastic change to suggest a folic acid deficiency and iron was abundant in the marrow fragments. Whilst it is tempting to postulate that protein deficiency may have contributed to the anaemia, it is more likely that blood volume changes associated with hypoalbuminaemia and oedema were a major factor.

Magnesium deficiency has recently been recorded in a patient who had gross steatorrhoea associated with a massive intestinal resection (Fletcher, Henly, Sammons, and Squire, 1960). In this patient the large amounts of fat excreted daily may have depleted the body by binding magnesium as soaps. It is interesting that in our patient, in whom steatorrhoea had been controlled by giving an extremely low-fat diet, the serum magnesium before death was normal.

The response of the human small intestine to resection has been studied in a large number of individual cases (Jackson, 1958) yet there is no unanimity of opinion as to whether the remaining intestine hypertrophies. In some instances, it has been stated that "compensatory" hypertrophy follows massive resection (Flint, 1912; Jackson, 1958) but in other cases no such hypertrophy has been observed (Shonyo and Jackson, 1950; Shelton and Blaine, 1954). Furthermore, in experimental animals the site of the resection may play a part in determining whether hypertrophy occurs (Booth, Evans, Menzies, and Street, 1959). In our patient, however, the necropsy specimen showed undoubted evidence of hypertrophy, for the calibre of the residual small intestine was considerably greater than that of a control and was in fact greater than that of the colon (Fig. 4). There was histological evidence of hypertrophy of the muscle layer and the mucosal cells showed many mitoses.

The extensive fatty change found in the liver (Fig. 5) is characteristic of patients who die after prolonged malnutrition (Dible, 1951). Similar fatty change after resection has been reported by Linder, Jackson, and Linder (1953). Pancreatic atrophy may sometimes be associated with intestinal resection in man (Linder *et al.*, 1953), but the pancreas was normal, possibly because the malnutrition had not been of sufficiently long duration. The tuberculous pericarditis and pleurisy found at necropsy were unexpected findings and may represent a long-standing tuberculous infection which had been reactivated during the period of malnutrition that preceded her death. In retrospect, it may have been significant that our patient's mother died of tuberculosis when her daughter was 5 years old.

We wish to thank Mr. Norman Tanner, F.R.C.S., for permission to give details of this patient while she was under his care; Dr. D. L. Mollin and Dr. I. Chanarin for the $B_{12}$ and folic acid absorption tests; Dr. I. McIntyre for the estimation of serum magnesium; and Professor C. V. Harrison for the necropsy report.

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# FACTORS INFLUENCING THE GROWTH OF *STAPHYLOCOCCUS AUREUS* IN THE STOMACH AFTER GASTRIC OPERATIONS

BY

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The frequency of post-operative staphylococcal invasion of the stomach appears to be related to the concentration of acid in the stomach. Evidence is presented suggesting that when it occurs such bacterial invasion may arise from the intestine rather than from the nose.

Acute entero-colitis as a complication of surgery was first recognized by Finney (1893) and somewhat later Riedel (1902) reported a personal series of five cases, describing the condition as a severe inflammatory process afflicting the bowel, characterized by the formation of a diphtheritic-like membrane on the wall of the gut from which Loeffler's bacillus could not be isolated. This acute intestinal inflammation develops most frequently between the third and second post-operative days, although occasional cases have been reported in which an interval as long as 39 days occurred between operation and the first manifestations of the disease. Many regard the condition as occurring primarily in the surgical patient, but Kleckner, Bargen, and Baggenstoss (1952) have also reported the syndrome in patients suffering from medical emergencies such as coronary thrombosis.

Normally the disease presents in one of two ways; either sudden torrential watery diarrhoea begins, the stools being likened to rice water, or alternatively vascular collapse occurs in a patient apparently convalescing normally after operation. It is this latter mode of presentation in patients who have undergone abdominal operations which leads to difficulties in diagnosis since many other causes of circulatory collapse exist in the early post-operative period.

When the disease became generally recognized there appeared to have been little doubt in the minds of those reporting these cases that the basic aetiological factor in this condition was an antibiotic-resistant *Staphylococcus aureus*. In more recent times, however, considerable doubt has been expressed as to the correctness of this hypothesis. Thus Dearing, Heilman, and Sauer (1954) stated that in the Mayo Clinic the incidence of post-operative entero-colitis had not risen following the introduction of antibiotics. Turnbull (1957) found that patients might die of fulminating staphylococcal lesions together with entero-colitis but from this latter lesion no staphylococci could be isolated even when using the most refined culture techniques. Weismann and Twitchell (1956) considered that the evidence in favour of the staphylococcus as the primary factor was weak and suggested that such pseudonyms as staphylococcal entero-colitis should not be used in the absence of concrete bacteriological and pathological evidence. With this view Kay, Richards, and Watson (1958) concur, and indeed these latter authors have separated the severe post-operative diarrhoeas into two groups: those in which the staphylococcus can be incriminated as the major cause of disease, *i.e.*, staphylococcal enteritis, and a second group, acute necrotising entero-colitis either patchy or diffuse, in which this organism, in their opinion, cannot be held responsible for the pathological changes. They point out that the differentiation of these two conditions is of considerable clinical importance since staphylococcal enteritis is potentially reversible if it is recognized early and treated effectively, whereas necrotising entero-colitis is a grave disease resistant to treatment and having a high mortality.

It is commonly assumed that the environment presented to bacteria by the highly acid gastric contents is inimical to bacterial growth. Bacteriological examination of the small bowel by Cregan and Maynard (1953) also showed that the jejunum and greater part of the ileum were without resident flora and practically sterile; nevertheless in staphylococcal enteritis the organism gains entrance into

the small bowel. There appears to be some doubt as to the route of infection. Brodie, Kerr, and Somerville (1956) found that faecal carriers of staphylococci were also nasal carriers and considered it likely that such organisms could ascend to the small bowel from the large as well as descend from the nasopharynx. Corridan and Shucksmith (1958) also considered that in their fatal case of post-operative enteritis in which staphylococci were cultured from the nasopharynx, stomach, and faeces, the route of infection had been from the colon.

It seems reasonable, however, to suppose that if staphylococci are present in the nasopharynx, an indwelling tube, such as is commonly used in the early post-operative treatment of the patient subjected to gastric surgery, might be the agent whereby the stomach, and thence the small bowel, becomes infected with this organism, particularly if the factors unfavourable to bacterial growth in the stomach have been removed or modified by the operation. The present investigation was designed to test this hypothesis. For this purpose the following information was secured on 44 consecutive patients admitted to the Professorial Surgical Unit: (*a*) The frequency with which staphylococci are present in the nasopharynx, (*b*) the incidence of colonization of the gastric remnant by staphylococci within the first 48 hours after operation, (*c*) the relationship of bacterial growth in the post-operative stomach to variations in the *p*H of the gastric contents, and (*d*) the occurrence of post-operative diarrhoea.

## Materials and Methods

The 44 patients were suffering from duodenal, gastric, or anastomotic ulceration, and the operations performed included resections of Polya or Billroth I type, or gastroenterostomy with or without vagotomy (Table I).

TABLE I

INDICATIONS FOR SURGERY AND OPERATION IN 50 CONSECUTIVE PATIENTS UNDERGOING GASTRIC OPERATIONS

| Indication for Operation | Operation Performed | | | |
|---|---|---|---|---|
| | Polya Resection | Billroth I Resection | Posterior Gastro-enterostomy | Posterior Gastro-enterostomy and Vagotomy |
| Duodenal ulcer | 28 | 1 | 1 | 3 |
| Prepyloric ulcer | 2 | 1 | — | — |
| Gastric ulcer | 3 | 4 | — | — |
| Anastomotic ulcer | 1 | — | — | — |

After admission to the wards nasal swabs were taken and sent for bacteriological examination with specific requests for information regarding the *Staphylococcus aureus* and its antibiotic sensitivity if present. On the morning of the day of operation, normally 24 hours after admission, a No. 10 F oesophageal tube was passed, and at laparotomy this was adjusted so that the open internal end lay within 1 in. of the stoma. Following operation the stomach or gastric remnant was aspirated every hour for 48 hours and the *p*H of the samples obtained was determined using a Pye Weston moving coil *p*H meter. The presence or absence of bile was also noted at this time. At 24 and 48 hours after operation a sterile polythene catheter was passed down within the lumen of the oesophageal tube and a small quantity of the gastric contents aspirated. These specimens were examined for staphylococci by culture on an 8% sodium chloride nutrient agar medium as well as on fresh blood and chocolate agar media, the two latter containing 10% horse blood. If *Staphylococcus aureus* was cultured the antibiotic sensitivity of the organism was determined by the punch plate technique at concentrations of 2 and 20 $\mu$g./ml. of a variety of antibiotics (Tables III and V).

## Results

BACTERIOLOGY OF THE NASOPHARYNX BEFORE OPERATION.—The nasal flora found pre-operatively in the patients of this series are shown in Table II.

TABLE II

BACTERIAL FLORA OF NASOPHARYNX IN 44 PATIENTS ABOUT TO UNDERGO GASTRIC OPERATIONS

| Organism Isolated | No. of Cases in which it was Grown |
|---|---|
| *Staph. aureus* coagulase positive | 21 |
| Diphtheroids or *staph. coagulase* negative | 23 |
| Other commensals | 17 |

From Table II it will be seen that in approximately 50% of all patients coagulase-positive staphylococci were isolated from nasal swabs. The sensitivity of these staphylococci to antibiotics is indicated in Table III, the isolated organism being insensitive in two-thirds of the cases to both penicillin and streptomycin. It will be noted further that in many of the cases the organisms were also resistant to aureomycin, and almost invariably they were sensitive to erythromycin. In two patients, however, the organism isolated was insensitive to the entire range of antibiotics listed in Table III.

TABLE III

ANTIBIOTIC SENSITIVITY OF COAGULASE-POSITIVE STAPHYLOCOCCI ISOLATED FROM NASOPHARYNX BEFORE OPERATION

| Antibiotic Tested | Sensitive | Insensitive | Unknown |
|---|---|---|---|
| Penicillin | In 4 patients | In 16 patients | In 1 patient |
| Streptomycin | In 2 patients | In 18 patients | In 1 patient |
| Aureomycin | In 4 patients | In 13 patients | In 4 patients |
| Chloromycetin | In 2 patients | In 9 patients | In 10 patients |
| Terramycin | In 5 patients | In 15 patients | In 1 patient |
| Erythromycin | In 15 patients | In 3 patients | In 3 patients |
| Novobiocin | In 12 patients | In 4 patients | In 5 patients |

Two coagulase-positive staphylococci were insensitive to all antibiotics in the above group.

BACTERIOLOGY OF POST-OPERATIVE STOMACH.—The bacterial flora on the first and second post-operative days are shown in Table IV. The

TABLE IV

BACTERIAL FLORA OF STOMACH IN 44 PATIENTS AFTER GASTRIC OPERATIONS

| Organism Grown from Gastric Aspirate | No. of Cases in which Organism was Isolated | |
|---|---|---|
| | First Post-operative Day | Second Post-operative Day |
| Staphylococcus | 22 | 11 |
| Coliform or proteus | 12 | 10 |
| Sterile | 10 | 23 |

stomach was sterile in only 10 of the 44 patients at the end of the first 24-hour period. In the remainder, evidence of bacterial invasion was found. Thus in 22 patients a coagulase-positive staphylococcus was found at the end of 24 hours and even at the end of 48 hours positive cultures of this organism were obtained in 11 patients. Coliform organisms or *B. proteus* were isolated in 12 patients at 24 hours and at 48 hours the gastric contents in 10 of these cases still contained these organisms.

The sensitivity of the staphylococci isolated from the post-operative stomach is shown in Table V. From this it will be seen that the majority of organisms were insensitive to all antibiotics other than erythromycin, as were the staphylococci isolated from the nasopharynx before the operation (Table II). The observation that staphylococci of similar sensitivity to antibiotics can be isolated from the post-operative stomach and from the nasopharynx before operation in an equal number of patients might suggest a close correlation between these two factors. On analysis, however, it was found that only nine of the 22 patients with positive staphylococcal nasal swabs developed positive gastric cultures for this organism at the end of the first post-operative day. In the other 13 patients in whom staphylococcal colonization occurred in the post-operative stomach at this stage, only commensals had been found in the nasopharynx.

*p*H OF CONTENTS OF POST-OPERATIVE STOMACH.—As regards the hydrogen ion concentration of the gastric contents during the 48 hours after operation, the cases have been divided into four groups according to the bacteriological state of the stomach as follows:—

*Group* 1.—Those patients in whom the stomach was sterile at both 24 and 48 hours after operation (10 patients).

*Group* 2.—Those in whom the stomach was colonized by coliform organisms or *B. proteus* at both 24 and 48 hours (12 patients).

*Group* 3.—Those patients in whom a coagulase-positive staphylococcus was present at 24 and 48 hours (11 patients).

*Group* 4.—Those in whom the staphylococcus was isolated at 24 hours but not at 48 hours (11 patients).

In order to simplify the presentation of results the *p*H value and presence or absence of bile in the gastric contents of each of these four groups of cases have been expressed not as an hourly determination, but as the findings on pooled hourly collections over six-hour periods. The results obtained are shown in graphic form in Fig. 1.

It will be seen that in Groups 2, 3, and 4 the hydrogen ion concentration of the gastric contents was low during the first 24-hour period as shown by *p*H readings in the neighbourhood of 7 and 8. Examination of the findings on individual patients confirmed these observations on the grouped cases. In Groups 2 and 3 the *p*H values of the gastric contents remained high during the second 24 hours also, but in Group 4 there was a striking fall in the *p*H during this second day. In the patients of Group 1 the *p*H was significantly lower (*p*H 4·0-5·6) during the first 24 hours than in the other three groups and this relatively greater gastric acidity continues in this group throughout the second 24 hours. The possible significance of this finding will be discussed below.

In the majority of patients bile was present within

TABLE V

SENSITIVITY TO VARIOUS ANTIBIOTICS OF COAGULASE-POSITIVE *STAPHYLOCOCCUS AUREUS* GROWN FROM POST-OPERATIVE STOMACH

| Antibiotic Used | Sensitivity of Organisms | | | | | |
|---|---|---|---|---|---|---|
| | First Post-operative Day 22 + ve Cultures | | | Second Post-operative Day 11 + ve Cultures | | |
| | Sensitive | Insensitive | Unknown | Sensitive | Insensitive | Unknown |
| Penicillin | 4 | 18 | 0 | 1 | 9 | 1 |
| Streptomycin | 2 | 18 | 2 | 1 | 7 | 3 |
| Terramycin | 3 | 17 | 2 | 0 | 10 | 1 |
| Chloromycetin | 3 | 11 | 2 | 0 | 10 | 1 |
| Erythromycin | 12 | 2 | 8 | 7 | 2 | 2 |
| Novobiocin | 9 | 2 | 11 | 6 | 3 | 2 |

FIG. 1.—
*after*
*in 12*
*in 11*
*hours*
*at 24*

INTRA GASTRIC pH.

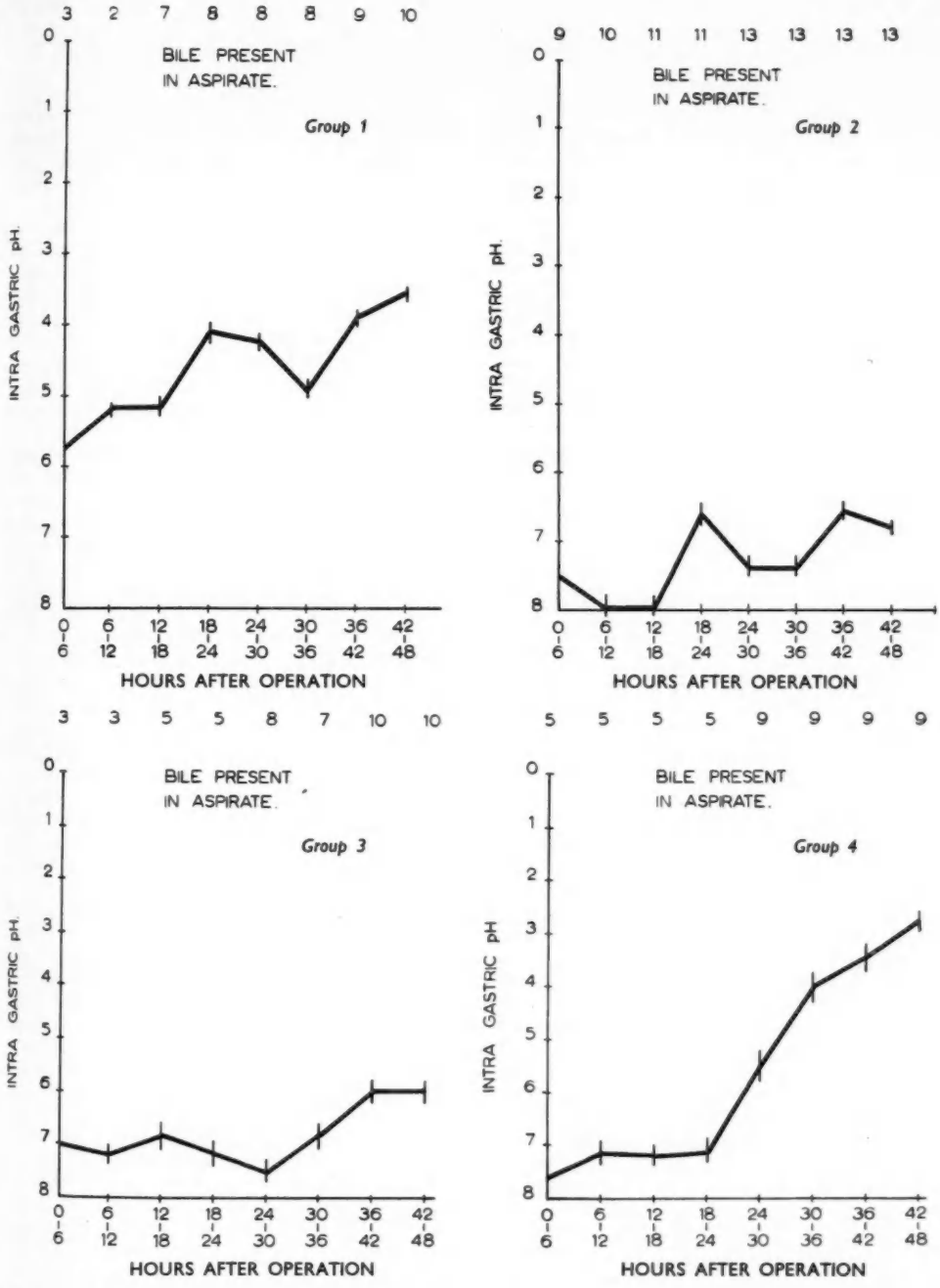


FIG. 1.—*The pH value and presence or absence of bile in the aspirates from the stomach during the first 48 hours after operation: in 10 cases in which the gastric contents were found to be sterile at 24 and 48 hours (Group 1); in 12 cases in which coliform organisms were found in the gastric contents at 24 and 48 hours (Group 2); in 11 cases in which coagulase-positive staphylococci were present in the gastric contents at both 24 and 48 hours (Group 3); and in 11 cases in which coagulase-positive staphylococci were found in the gastric aspirate at 24 hours but not at 48 hours (Group 4).*

the remnant or stomach by the end of the first day, the frequency of bile-staining of aspirated contents being approximately equal in all four groups.

DEVELOPMENT OF DIARRHOEA.—During the present study four patients had mild diarrhoea, seldom amounting to more than three or four motions a day. In each of the four the diarrhoea began during the fourth post-operative day, in one patient lasting for 24 hours, in two for 48 hours, and in the fourth patient for three days. After the passage of the first liquid motion the anus was swabbed and cultures of the next bowel action were made. A culture positive for *Staphylococcus aureus* was obtained in one patient. In none of the four patients was immediate or late treatment with erythromycin considered necessary and in all patients the diarrhoea terminated spontaneously.

## DISCUSSION

It is generally considered that the normal stomach is sterile except for a transient bacterial flora found soon after eating when the food contaminated by contact with the mouth infects the cavity. Sterility, however, may be lost in the presence of a malignant tumour or some alteration of mobility such as is found in pyloric stenosis (Oppler, 1895). In the small bowel, Cregan and Maynard (1953) found that the upper jejunum and midgut were also sterile, no growth occurring from 22 out of 28 samples taken from these sites at operation in patients with normal gastrointestinal tracts. In addition they found that in 12 out of 14 cultures taken from the lower ileum a mixed flora of such low growth intensity occurred that they regarded such bacteria as transient rather than resident. Thus there remain two potential bacterial reservoirs in man, the nose and mouth at the upper end, and, at the lower end, the colon.

There appear to be at least three mechanisms whereby the stomach and small bowel remain sterile in spite of the presence of these reservoirs of infection at either end of the alimentary tract. First, the gastric acidity: to initiate a growth of coliform or coagulase-positive staphylococci a *p*H of between 7·4 and 7·6 is required, but once initiated growth may proceed even in the presence of hydrogen ion concentrations as great as *p*H 4·0-5·0 (Wilson and Miles, 1955). Arnold and Brody (1926) also consider that the "auto-disinfecting" mechanism of the duodenum and jejunum is dependent upon acid derived from the stomach, since in this area the normal hydrogen ion concentration lies between 5·5 and 6·3, a concentration dependent upon the delivery of acid-buffered material from the stomach. Two further factors, however, are involved: first, the entrapping of bacteria by the lace-like network of mucus and, secondly, the onward passage of such mucus by normal peristaltic action which, in turn, diminishes retrograde infection of the lower ileum from the large bowel (Florey, 1933).

When a gastric operation is performed at least two of these normal mechanisms of "auto-disinfection" are disturbed. Since all gastric operations are designed to bring about a fall in acid secretion by one or more means, the level of acidity in various parts of the bowel changes with special emphasis on the alteration of the intragastric hydrogen ion concentration. The evidence produced here shows that without exception depression of acid secretion is constantly present on the first post-operative day. In some patients high hydrogen ion concentrations reappear on the second day. Later during convalescence free acid, *i.e.*, *p*H greater than 3·5, is found in the majority of patients (Smiddy, 1957). This lowering of the intragastric acidity, together with its effect on the intestinal acidity, appears, from the data presented, to be the factor determining bacterial invasion of the stomach or gastric remnant following operation. In those patients in whom an intragastric acidity of between 6·5 and 8·5 was found coliform or coagulase-positive staphylococci were isolated from gastric aspirates. In those in whom a higher hydrogen ion concentration was present, *p*H range 5·5-3·5, the stomach remained sterile, and in those in whom staphylococci were present on the first day a marked rise in intragastric acidity appeared to sterilize the remnant during the second post-operative day. The presence or absence of bile in the stomach does not seem to bear any relation to bacterial invasion.

Although this evidence allows one to assume then that the stomach in some 50% of patients will be colonized by staphylococci within 24 hours of a gastric operation, it does not answer the question as to the source of infection. Two alternative routes of infection are possible, downwards from the nose, or upwards from the bowel. The finding that, in keeping with the nasal carrier rate of *Staphylococcus aureus* in the general population, approximately 50% of patients in this series had positive nasal swabs soon after admission is consistent with a descending route of infection, since from 50% of patients staphylococci can be grown from the stomach within 24 hours of operation. This hypothesis is supported by the almost identical sensitivity and resistance patterns of the staphylococci isolated but seems to be rendered completely invalid by the fact that in more than half the patients in whom staphylococci were isolated from gastric aspirates, no staphylococci were present

pre-operatively in the nose. Furthermore, the presence of coliform organisms in the stomach remnant cannot be explained in terms of downward spread of bacteria from the nasopharynx. It would appear reasonable to assume that the gastric invasion with the coliform group occurred by retrograde spread from the lower bowel and it is, therefore, not unlikely that staphylococci ascended by this route also. There can be no doubt that conditions in the bowel post-operatively would favour retrograde spread. First, intraluminal acidity is altered in favour of bacterial growth and secondly, intestinal peristalsis is diminished, thus removing the factor of onward passage of entrapped bacteria in the mucus lacework. To substantiate this hypothesis of retrograde infection it would be necessary to phage-type the nasal, intragastric, and colonic staphylococci isolated; this unfortunately was not done in this study.

Has this staphylococcal colonization of the post-operative stomach any significance in regard to the development of pseudo-membranous entero- colitis? The fact that none of the patients studied in this enquiry, and particularly none of those in the group with staphylococci in the gastric contents post-operatively, developed typical entero-colitis, certainly seems to belittle the importance of gastric infection of this kind in the aetiology of this complication. It has also to be remembered that in ordinary surgical practice many of the patients who develop entero-colitis have not had a gastric operation and presumably retain normal conditions of acidity in the stomach which are inimical to the growth of organisms there.

One further point deserves comment. The high incidence of resistance of both nasal and gastric staphylococci isolated in this series to all antibiotics other than erythromycin reinforces the argument that the "prophylactic" use of penicillin and streptomycin in the early post-operative phase should be abandoned and that infections developing during the course of convalescence should be treated with antibiotics appropriate to the predetermined sensitivity of the organism.

## Conclusion

It has been shown that 50% of a group of patients admitted for gastric operations harbour *Staphylococcus aureus* in the nose immediately after entry to hospital, and that many of these organisms are highly resistant to the commonly used antibiotics, penicillin and streptomycin. In some 50% of this same group of patients strains of *Staphylococcus* were isolated from the stomach contents 24 hours after operation, but it was usually patients who had had negative pre-operative nasopharyngeal swabs who developed such gastric infestation. The frequency of post-operative staphylococcal invasion of the stomach appears to be related to the intragastric hydrogen ion concentration, since in-patients in whom a relatively high degree of acid secretion returns during the second post-operative day the gastric contents are invariably found to be sterile. The frequent presence of coliform organisms in the post-operative stomach, along with staphylococci, suggests that the bacterial invasion of the stomach is from the intestine rather than from the nose.

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# GASTRIC ACTIVITY IN THE SOUTH AFRICAN EUROPEAN AND BANTU

BY

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Test meals in Europeans and Bantu in Johannesburg show that the stomachs of normal Europeans in the main secrete more acid and pepsin.

Gastric studies in Bantu on a European diet compared with those on a more non-European type of diet reveal no difference in secretory behaviour. This, it is suggested, rules out current dietary habits as being responsible for the difference in gastric secretory behaviour found between European and Bantu.

The Bantu on a European diet had a slower rate of gastric emptying than those on a non-European diet.

The incidence of peptic ulceration is low in the South African Bantu as compared with the European living in that country. Eagle and Gillman (1938), as a result of examining Government and hospital post-mortem records in South Africa, declared that the European is apparently seven times more susceptible to peptic ulcer than the Bantu. Many factors may contribute to this difference in incidence of peptic ulceration and it was felt that it would be useful to know the gastric "background" upon which the factors responsible for ulceration had to operate.

## METHODS

The subjects were volunteers from three groups of persons. One group consisted of 11 medical students of European ancestry aged 19-21 years, a second group was made up of nine Bantu laboratory assistants aged 25-39 years working in the department, while the third group contained eight Bantu undergraduates aged 18-26 years.

Each subject was given a test meal on three successive days after fasting for 12 hours. The composition of the test meals and the order of their ingestion were as follows:—

(1) 750 ml. of a solution containing 35 g. sucrose/litre
(2) 750 ml. of distilled water
(3) 750 ml. of a solution containing 100 mEq. saline/litre

These three meals were chosen because they produce three grades of emptying due to variations in their influence upon the duodenal receptors which act as brakes on gastric outflow.

(1) The sucrose has a marked action upon duodenal receptors and slows the emptying of the stomach, *i.e.*, prolongs the period of gastric distention.

(2) Distilled water exerts a moderate influence on duodenal osmo-receptors in that the emptying is faster than with the sucrose meal.

(3) The saline meal exerts a minimal influence on duodenal osmo-receptors, and the rate of gastric emptying is therefore the fastest of the three (Hunt, 1956).

Each meal also contained phenol red which was used as an indicator of the dilution of the gastric contents (Hunt and Spurrell, 1951). Before each meal a tube was passed and the stomach washed out with tap water. The meal was then given down the tube direct into the stomach. All the saliva was aspirated during the period of ingestion. The whole of the gastric contents was recovered after 30, 20, and 10 minutes' ingestion of the sucrose, water, and saline meals respectively.

The estimations and calculations used were those described by Hunt and Spurrell (1951) except that pepsin was estimated by the method of Anson and Mirsky (1932).

## RESULTS

These are seen in Table I and are expressed as mean values together with the standard deviation for each group and each type of meal. Table II gives the $p$ values when the findings in the Bantu groups are compared with those in the European group.

RATE OF EMPTYING.—Since meals were of known volume (750 ml.) the volume of a meal remaining at the end of the experimental period was taken as an index of the emptying rate during that period. The volume of a meal remaining was estimated by

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TABLE I

MEANS AND STANDARD DEVIATIONS OF DATA FROM THREE TYPES OF TEST MEAL IN THREE GROUPS OF SUBJECTS

| Meal | Sucrose | | | Water | | | Saline | | |
|---|---|---|---|---|---|---|---|---|---|
| | Europeans | Bantu Laboratory Assistants | Bantu Under-graduates | Europeans | Bantu Laboratory Assistants | Bantu Under-graduates | Europeans | Bantu Laboratory Assistants | Bantu Under-graduates |
| Mean volume of meal remaining (ml.) | 285 | 201 | 303 | 377 | 276 | 321 | 433 | 278 | 473 |
| S.D. | ± 103 | 121 | 68 | 101 | 95 | 63 | 101 | 134 | 68 |
| Mean concentration of $H^+$ (mEq./l.) in gastric contents | 13·1 | 6·9 | 7·0 | 10·9 | 7·7 | 6·2 | 5·1 | 3·4 | 2·5 |
| S.D. | ± 8·2 | 4·7 | 5·3 | 7·1 | 4·7 | 3·8 | 3·2 | 2·0 | 2·1 |
| Mean concentration of $Cl^-$ (mEq./l.) in gastric contents | 24·9 | 18·2 | 15·8 | 16·1 | 14·6 | 12·6 | — | — | — |
| S.D. | ± 13·3 | 7·7 | 3·2 | 8·6 | 5·7 | 3·4 | — | — | — |
| Mean concentration of pepsin (mg. tyrosine/l.) in gastric contents | 17·1 | 10·4 | **6·8** | 13·3 | 7·6 | 8·8 | 10·6 | 8·8 | **4·2** |
| S.D. | ± 8·8 | 7·0 | 5·3 | 7·1 | 4·2 | 4·1 | 6·1 | 5·5 | 4·3 |
| Mean amount of $H^+$ (mEq.) | 8·0 | 4·0 | 4·3 | 6·3 | 4·4 | 3·7 | 3·7 | 2·0 | 1·8 |
| S.D. | ± 5·3 | 2·6 | 3·2 | 4·2 | 2·7 | 2·2 | 2·3 | 1·1 | 1·5 |
| Mean amount of $Cl^-$ (mEq.) | 15·3 | 10·5 | 9·5 | 10·1 | 8·6 | 7·3 | — | — | — |
| S.D. | ± 8·1 | 4·5 | 2·1 | 5·2 | 3·7 | 1·9 | — | — | — |
| Mean amount of pepsin (mg. tyrosine) | 10·5 | **6·0*** | **4·1** | 8·1 | 4·5 | 5·1 | 6·9 | 5·2 | **2·8** |
| S.D. | ± 5·3 | 3·6 | 4·3 | 4·0 | 2·5 | 2·4 | 4·1 | 3·4 | 3·1 |

*Values where the significance of the difference from the European group is greater than 1 in 20 are in bold type.

TABLE II

VALUES OBTAINED BY COMPARISON OF MEANS FROM EUROPEAN GROUP WITH TWO BANTU GROUPS

| Responses to Test Meals in European Group Compared with | Vol. of Meal Remaining | $[H^+]$ | Amount $H^+$ | $[Cl^-]$ | Amount $Cl^-$ | [Pepsin] | Amount Pepsin |
|---|---|---|---|---|---|---|---|
| *Sucrose Meal* | | | | | | | |
| (*a*) Bantu laboratory assistants | 0·1 | 0·1—0·05 | 0·1—0·05 | 0·3 | 0·2—0·1 | 0·1 | 0·05 |
| (*b*) Bantu undergraduates | 0·5 | 0·1 | 0·1—0·05 | 0·1—0·05 | 0·1—0·05 | **0·01** | **0·01** |
| (*c*) Groups (*a*) and (*b*) combined | 0·4 | **0·025** | **0·025—0·01** | **0·05** | **0·025** | **0·005** | **0·005—0·001** |
| *Water Meal* | | | | | | | |
| (*a*) Bantu laboratory assistants | **0·05** | 0·3 | 0·4—0·2 | 0·6 | 0·5—0·4 | **0·05** | **0·05—0·025** |
| (*b*) Bantu undergraduates | 0·2 | 0·1 | 0·2—0·1 | 0·3 | 0·2—0·1 | 0·2—0·1 | 0·1—0·05 |
| (*c*) Groups (*a*) and (*b*) combined | **0·05** | 0·1 | 0·1 | 0·3 | 0·2 | **0·025** | **0·01** |
| *Saline Meal* | | | | | | | |
| (*a*) Bantu laboratory assistants | **0·005** | 0·2 | 0·1—0·05 | — | — | 0·5 | 0·4—0·2 |
| (*b*) Bantu undergraduates | 0·3 | 0·1—0·05 | 0·1—0·05 | — | — | **0·025** | **0·025** |
| (*c*) Groups (*a*) and (*b*) combined | 0·2 | **0·05—0·025** | **0·025—0·01** | — | — | 0·1—0·05 | **0·05** |

A significance greater than 1 in 20 is shown in bold type.

multiplying the volume of the gastric recovery by the percentage of the marker dye, phenol red, in the recovery.

There was no difference between the groups in the volume of test meal remaining after the sucrose meal. With the water and saline meals the Bantu laboratory assistants had a significantly smaller volume of the meal remaining than the Europeans, but this was not so with the Bantu undergraduates (Fig. 1). One striking feature of the gastric findings was that in response to the sucrose and saline meals the Bantu undergraduates had a significantly larger volume of meal remaining than the Bantu laboratory assistants, this being the only difference in gastric behaviour found between the two Bantu groups.

CONCENTRATION OF $H^+$.—There was a tendency for the Bantu to have a lower $H^+$ concentration in the gastric contents than the Europeans. If, however, the $H^+$ concentrations of the two Bantu groups are combined and the mean value of the combination compared with the mean European $H^+$ concentration, then a lower $H^+$ value is shown by the Bantu for the sucrose and saline meals, the difference being statistically significant.

AMOUNT OF $H^+$.—The amount of $H^+$ secreted in response to a test meal has been calculated from the amount in the gastric contents with the addition of an amount derived from the calculation of the volume of gastric contents passing the pylorus. The amount of $H^+$ thus calculated is lower in response to the sucrose and saline meals in each Bantu group than in the European group ($P = 0{\cdot}1 - 0{\cdot}05$) but responses to water meals show no difference (Fig. 2).

CONCENTRATION OF CHLORIDE.—No estimation of chloride ($Cl^-$) was made in the response to the saline meal. With the other two meals the comparison between the European and Bantu groups show that, like the $H^+$ concentration, the $Cl^-$ concentration tends to be less in the Bantu in response to the sucrose meal, a difference which is statistically significant if values from both Bantu groups are

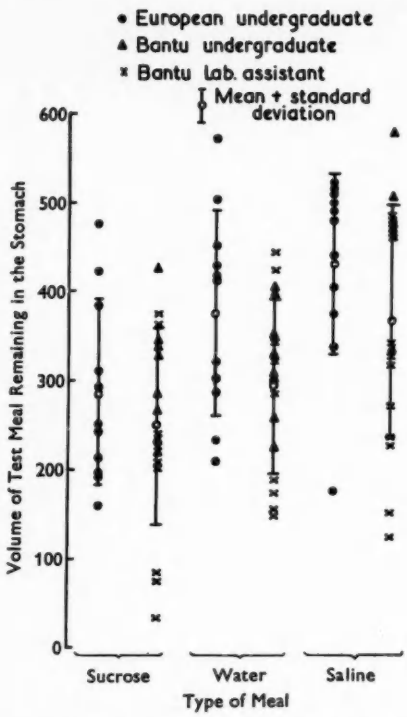


FIG. 1.—*Volume of test meal remaining in the stomach plotted against the type of meal for each racial group.*

combined, whereas no difference is seen in the $Cl^-$ concentration of the racial groups in response to the water meal.

AMOUNT OF CHLORIDE.—The amount of $Cl^-$ tends to be less in both Bantu groups than in the European group, in response to the sucrose meal, a difference which becomes statistically significant when the two Bantu groups are combined. No difference in the amount of $Cl^-$ secreted is seen in the responses to the water meal (Fig. 3).

CONCENTRATION OF PEPSIN.—The concentration of pepsin tends to be less in the gastric response of both Bantu groups than in the European, and when the combined Bantu group is compared with the European group the difference becomes statistically significant in response to the sucrose and water meals and in the saline meal the value of P is 0·1 — 0·05.

AMOUNT OF PEPSIN.—The amount of pepsin was significantly less in each Bantu group in every meal except the Bantu undergraduates' response to the water meal and the Bantu laboratory assistants' response to the saline meal. All the combined Bantu group mean pepsin amount was less than that in the European group (Fig. 4).

## DISCUSSION

The results show that the Bantu secrete less acid and pepsin than the Europeans under similar circumstances, and also that the Bantu have lower concentrations of acid and pepsin in the gastric contents. If the concentration of $H^+$ and pepsin must reach a certain level before duodenal ulceration can occur then the Bantu are further away from this level than the Europeans and would require a greater secretory effort to reach the threshold of duodenal trauma. This may be one reason why duodenal ulceration is apparently less frequent in the South African Bantu compared with the Europeans in the same region.

Direct comparative studies with Europeans have not been done but Barnes and Gordon (1937) found a tendency to a lower acidity of gastric contents in

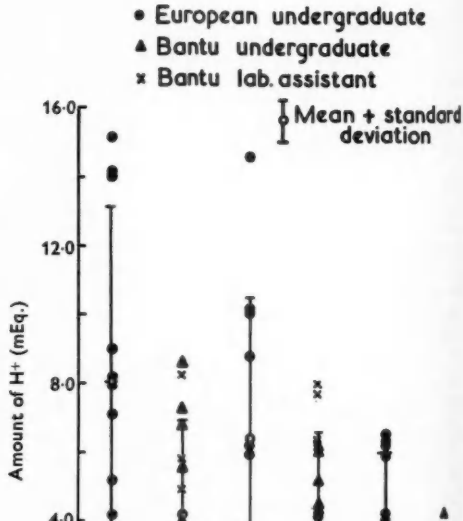


FIG. 2.—*Amount of $H^+$ plotted against the type of meal for each racial group.*

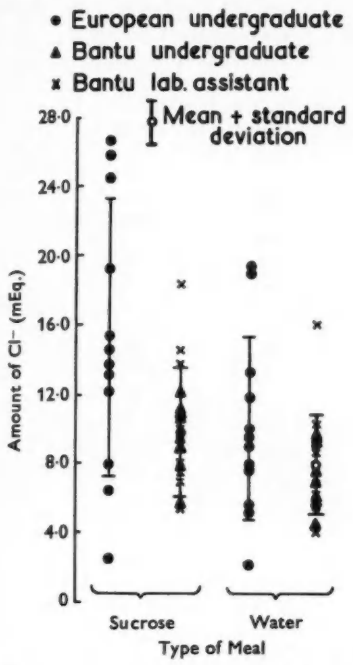


FIG. 3.—*Amount of $Cl^-$ plotted against the type of meal for each racial group.*

the South African Bantu than that usually found in similar tests on Europeans, whereas normal Bantu in southern Nigeria (Ellis, 1934) had a mean "free acid" very similar to that described in European medical students by Bennett and Ryle (1921).

The individual measurements obtained here cannot be compared with those obtained by fractional test meals, though the results from southern Nigeria suggest no racial difference as compared with the European. However, the response (except pepsin) to the water and saline meals can be compared with the findings in male medical students in London described by Booth, Hunt, Miles, and Murray (1957). The mean values of these workers' findings are all lower than those in the European undergraduates in Johannesburg, but higher than in the Bantu group. The significance of this finding is not clear.

If it is not genetics that accounts for the lower acid and pepsin production of the stomach of the South African Bantu, then can it be that diet is responsible ?

It was for this reason that the gastric behaviour of the Bantu undergraduates was studied. The difference in gastric activity that was apparent between the Europeans and the Bantu laboratory assistants might have been due to diet, therefore the Bantu undergraduates were examined as they all lived in residence on a European diet. In actual fact no difference was found in the gastric secretory response between the two Bantu groups. As the undergraduates had been in residence for periods from six months to three years with breaks for vacation, and as the previous vacation away from the residence was approximately six months before the test meals in most of the Bantu undergraduates, whereas the laboratory assistants lived in their own quarters, it can be concluded that current dietary habits played no significant part in determining the gastric secretory response to test meals.

With regard to the rate of gastric emptying as assessed by the volume of test meal remaining, there are in the sucrose and saline meals significant

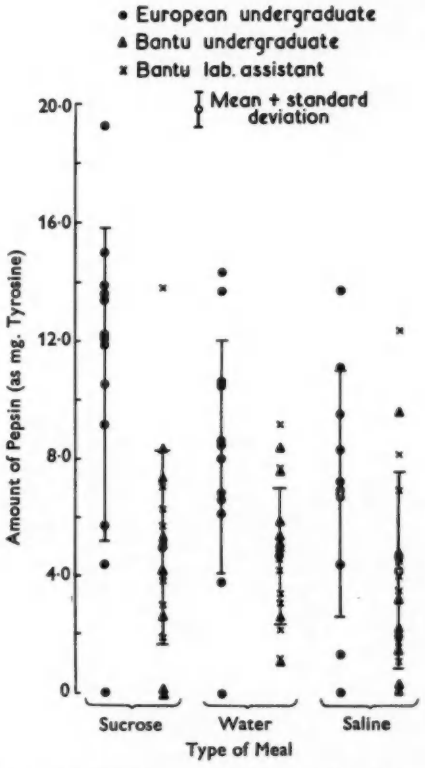


FIG. 4.—*The amount of pepsin plotted against the type of meal for each racial group.*

differences in response between the two Bantu groups, the undergraduate group having values approximating those found in the European undergraduates. This difference may well be dietetic, not so much in the composition of the diet perhaps but in the volume normally consumed. The meals of the laboratory assistants tend to be more bulky than western diets and this may be responsible for the more rapid gastric emptying seen in the laboratory assistant group.

Konstam (1954) believes that diet plays an important role in the pathogenesis of duodenal ulcer, and it has been shown by using fractional test meals (Ellis, 1934; Konstam, 1955) that ulcer patients in southern Nigeria have a higher free acid than controls. Therefore, by implication, the diet would appear to be associated with the degree of acidity of gastric contents. Rose (1935), also using fractional test meals, found that many natives of northern Nigeria exhibit a degree of acidity which is high compared with European standards, and he suggested that this difference in level of acidity is dietary in origin. In the present series it does not appear that a direct and immediate effect of diet influences gastric secretory activity, as the Bantu undergraduates who have been on a European diet do not show gastric secretory activity similar to that in the Europeans but rather like that in the Bantu laboratory assistants whose diet consists largely of maize.

I am most grateful to the volunteers who made this work possible. I also wish to thank Mr. A. Martin for assistance with the pepsin estimations and the Peel Trust Fund of the Medical Research Council of Great Britain for a grant towards costs of travel.

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*Gut*, 1960, **1**, 253.

# BENIGN DUODENO-COLONIC FISTULA

BY

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Two cases of benign duodeno-colic fistula are described. In the first, no cause was evident, but complete cure of an illness characterized by fatty diarrhoea, loss of weight, anaemia, and osteomalacia followed surgical repair. In the second patient cure was spontaneous after a peri-duodenal abscess from a perforated post-bulbar duodenal ulcer discharged into the hepatic flexure of the colon.

Duodeno-colic fistula is an uncommon lesion which usually results from the extension of carcinoma from the transverse colon. Benign causes of the condition are exceedingly rare and only 21 examples, of diverse aetiology, have been recorded since 1863. The commonest single cause is peptic ulceration of the duodenum; McPeak (1940) presented two such cases, and single case reports were made by McClinton (1944), Railton (1948), Rife (1951), and Nash and Daland (1956).

The earliest recorded example is that of Sanderson (1863) who reported a patient with a fistula between the descending duodenum and the mid-transverse colon, probably the result of a perforating diverticulum of the duodenum. In a patient of Olson's, originally described by Krock (1950), the most likely cause of a fistula connecting the second part of the duodenum and the hepatic flexure of the colon was thought to be a diverticulum of the duodenum, and a third such case was reported by Winter (1959). Rees (1933) reported a fistula between the transverse colon and the duodenum just below the opening of the common bile duct, which had apparently arisen by the perforation of a typhoid ulcer 28 years previously. Ogilvie (1950) reported two cases of benign duodeno-colic fistula which appeared to have originated from a caseating tuberculous gland that had ulcerated simultaneously into the two viscera. Winfield (1951) recorded another example in which tuberculous lymphadenitis appeared to be the cause of a fistula between the third part of the duodenum and the sigmoid colon.

In three patients the condition occurred as a complication of ulcerative colitis. Ormandy and Bargen (1939) recorded the necropsy finding of multiple fistulae between the colon and the stomach and duodenum in a patient who died from ulcerative colitis. Ransom (1951) described two patients with colitis and fistulous connexions between the duodenum and transverse colon who made an uneventful recovery after subtotal colectomy and closure of the duodenum. Examples of the condition following attacks of acute cholecystitis were reported by Lovell (1947) and Neville (1954), and duodeno-colic communications have been recorded in acute pancreatitis (Garland and Wyatt, 1951), in acute appendicitis (Clayton and Thornton, 1953), and in regional ileitis (Masters, 1948). Michell (1959) described a patient in whom the fistula developed after gastrectomy.

This paper reports two more examples of the condition. In one patient the clinical picture simulated that of the blind loop syndrome and is the first in which steatorrhoea has been recorded. The second patient presented as an acute abdominal emergency.

## Case Reports

Case 10.—An unmarried woman, in comfortable circumstances, was aged 51 years at the time of her admission to the General Infirmary at Leeds in July, 1956. Seventeen years previously a diagnosis of pernicious anaemia had been made on the basis of a peripheral blood examination following a short history of diarrhoea with the passage of loose, pale stools and the constitutional symptoms of anaemia. She was unable to recall any episode of abdominal pain. She had been given regular injections of liver extract and more recently had been treated with vitamin B.12. Her health remained good until 1954 when she began gradually to lose energy and appetite; her weight fell by nearly 50 lb. (22·7 kg.) in the ensuing two years. Diarrhoea again became troublesome with the passage of four or five loose, watery motions daily. Because of the development of pain about the knees and ankles associated with swelling of the feet and exertional dyspnoea she was referred to the Rheumatism Clinic and admitted under the care of Prof. S. J. Hartfall for further study.

FIG. 1.—*Barium enema examination (Case 1). Note presence of barium in the stomach.*

FIG. 2.—*Barium meal examination (Case 2). Presence of fistula between duodenum and colon confirmed. The communication appears to arise at the outer border of the junction of the second and third parts.*

Examination disclosed a thin but active woman. She was edentulous but the tongue and nails were normal. Both lower legs were oedematous and the skin showed pigmentation associated with superficial periphlebitis. The abdomen was distended and the liver and spleen enlarged two fingerbreadths below the costal margin. There was no neurological defect. The stools were loose, pale, and somewhat greasy.

Investigations gave the following results: haemoglobin 78% (11·5 g. per 100 ml.); M.C.V. 97 cu, M.C.H.C. 31%; colour index 1·0; white blood cells 4,500 per c.mm.; total serum proteins 6·2 g. per 100 ml. (albumin 3·8 g. and globulin 2·4 g. per 100 ml.); gold sol negative; thymol turbidity 2 units; prothrombin time 14 seconds (control 13 seconds); serum calcium 8·1 mg. per 100 ml.; serum phosphate 3·2 mg. per 100 ml.; serum alkaline phosphatase 40 King-Armstrong units; serum sodium 139 mEq. per litre, serum potassium 3·6 mEq. per litre; serum chloride 109 mEq. per litre; plasma $CO_2$ 21·5 mEq. per litre; sternal marrow puncture showed normoblastic erythropoiesis and normal levels of acid secretion were found by fractional test meal examination. A radiograph of the chest revealed only skeletal decalcification. A barium enema demonstrated the presence of a fistula between the duodenum and hepatic flexure of the colon (Fig. 1), which, on barium meal examination appeared to arise at the junction of the second and third parts of the duodenum (Fig. 2). A three-day fat balance study showed a faecal fat excretion of 37% of dietary intake.

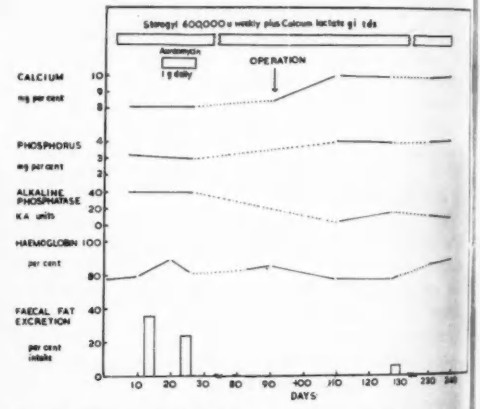


FIG. 3.—*Effect of* (a) *chlortetracycline and* (b) *repair of the fistula on faecal fat excretion, haemoglobin percentage, and serum levels of calcium, phosphorus, and alkaline phosphatase in Case 1. During treatment with aureomycin faecal fat loss fell from 37% to 24% of dietary intake. Repair of the fistula abolished steatorrhoea, corrected the anaemia, and restored normal serum chemistry.*

Treatment with vitamin B.12 was stopped from admission but because of the evidence of osteomalacia she was given vitamin D ("sterogyl"), 600,000 units

weekly by intramuscular injection, and calcium lactate, 1 g. t.d.s. During a period when chlortetracycline, 250 mg. q.d.s., was administered by mouth, a second fat balance study was made; this showed a reduction in faecal fat excretion to 24% of intake.

At operation in August, 1956, Professor J. C. Goligher found a fistula connecting the junction of the second and third parts of the duodenum with the hepatic flexure of the colon. There was no evidence of local disease and the remainder of the abdominal organs appeared healthy. Closure was easy and the patient's post-operative recovery was rapid and uneventful. The diarrhoea ceased entirely and a third fat balance study done two months after operation showed normal fat absorption (Fig. 3). The serum levels of calcium, phosphorus, and alkaline phosphatase also returned to normal and the limb pains disappeared. Within six months of operation the patient had gained 40 lb. (18·2 kg.) in weight and the treatment with calcium and vitamin D was discontinued. She has been reviewed at annual intervals and remains delighted with her sustained improvement.

This was an example of benign duodeno-colic fistula of at least 17 years' duration. No cause for its development could be demonstrated. The patient presented with diarrhoea of fatty type, considerable loss of weight, and osteomalacia. The steatorrhoea was reduced by oral antibiotic treatment and abolished by repair of the fistula. Complete cure resulted from operation.

FIG. 4.—*Barium meal examination (Case 2). The duodenal cap is somewhat deformed and immediately distal to it the upper two-thirds of the second part of the duodenum becomes grossly irregular in outline. Note ulcer crater on the concavity of the loop at the junction of the first and second parts of the duodenum.*

FIG. 5.—*Barium meal examination (Case 2). Later film shows filling of the duodenum from the colon and a collection of barium in a mass separating these two structures. Note shaggy outline of the hepatic flexure of the colon.*

CASE 2.—A 58-year-old man of Anglo-Indian extraction was admitted to the Central Middlesex Hospital on September 12, 1959, because of abdominal pain. In 1939, he had been treated for amoebic dysentery in India; later that year he had developed dyspepsia of duodenal type and a diagnosis of duodenal ulcer had been made. With conventional medical treatment for his ulcer he had remained in excellent health until the day before admission when he took a purgative for constipation. Seven hours later he was seized with severe epigastric pain radiating into the right hypochondrium associated with the passage of loose, watery stools.

By the time of admission the pain had lessened and he did not seem acutely ill. His temperature was 100·2°F. and pulse rate 100 per minute. The abdomen was generally tense but nowhere rigid, and there was tenderness on palpation of the right upper quadrant. There was no other abnormality in any system. A plain film of the abdomen was normal, white cell count was 10,500 per c.mm., and bacteriological examination of the stools was negative. Sigmoidoscopy was normal to 25 cm.

During the first week of illness he complained of abdominal pain of no great severity and his temperature, at first intermittent, gradually rose to between 102°F. and 103°F. Diarrhoea meanwhile had lessened to average four loose motions daily without blood. On the eighth day after admission a firm, rounded mass could be felt in the right hypochondrium, and the white cell count had risen to 28,000 per c.mm. Liver function tests showed no abnormality except for a modest elevation of serum bilirubin to 1·5 mg. per 100 ml. Oral cholecystography showed no excretion of dye in the biliary system but barium meal examination on the tenth day of illness revealed a deformed duodenal cap with an ulcer crater just distal to it on the concavity of the loop at the junction of the first and second parts. The second part of the duodenum was compressed from its outer side and displaced forwards by a mass which was bounded superiorly by the right lobe of the liver. The hepatic flexure of the colon was grossly irregular in outline and lay on the outer side of the mass. In subsequent films there was a collection of barium in the mass, shown only in films in which the colon was outlined (Figs. 4 and 5).

Treatment with tetracycline, 250 mg. q.d.s., was begun 11 days after admission with prompt response; temperature fell to normal after 24 hours and the mass gradually diminished and finally disappeared within seven days, during which time the diarrhoea ceased. Subsequent re-examination by barium meal showed that the ulcer crater was still visible but no mass could be demonstrated and no escape of barium was seen.

The patient returned home one month after admission. He was active, ambulant, and afebrile. No abnormal physical signs remained and bowel function was normal.

This was an example of a benign duodeno-colic fistula consequent on the perforation of a post-bulbar duodenal ulcer. The patient presented with an acute abdominal illness characterized by fever, diarrhoea, and abdominal pain. An inflammatory mass developed in the right sub-hepatic space which was shown to communicate with the colon by barium meal examination. Its subsequent discharge into the colon led to spontaneous cure.

## Discussion

Of the various causes of benign duodeno-colic fistula performation of a duodenal ulcer is the most common, and is followed in frequency by ulcerative colitis and tuberculous lymphadenitis. In our first patient no cause was evident, but the situation of the fistula, which connected the junction of the second and third parts of the duodenum with the hepatic flexure, suggested the possibility that a foreign body might have been responsible. In the habit of making her own dresses she might have swallowed a needle or pin which, impacted at this particular curve of the duodenum, had gradually penetrated the colon and finally disappeared leaving only a fistulous track to mark its passage.

Diarrhoea is an almost inevitable sequel to the establishment of such a fistula, but in none of the reported cases with a benign aetiology has steatorrhoea been described. Mindline and Rosenheim (1935) reported an example of duodeno-colic fistula caused by carcinoma of the transverse colon in which the clinical picture simulated that of idiopathic steatorrhoea. It has long been recognized that any intestinal lesion causing stasis within the lumen of the gut as from stricture formation or by the production of a redundant loop of bowel could lead to the development of a syndrome characterized by diarrhoea, loss of weight, and macrocytic anaemia. Now known as the blind loop syndrome, the subject was reviewed by Cameron, Watson, and Witts (1949a). Of 61 patients, 24 had entero-anastomoses, nine of which were either gastro-colic or high jejuno-colic fistulas. Halsted, Lewis, and Gasster (1956) were able to collect 76 cases from the literature and added three of their own. Simple exclusion of a large part of the small intestine might be expected, on purely mechanical grounds, to lead to faulty absorption and a deficiency syndrome, but changes in the bacterial flora of the bowel are probably of greater significance. Cameron *et al.* (1949b) were able to produce a macrocytic anaemia in rats, sometimes associated with steatorrhoea, by fashioning blind loops in the small intestine. These intestinal cul-de-sacs were antiperistaltic and therefore self-filling to encourage stasis. In later work Watson and Witts (1952) showed that the anaemia so produced responded well to folic acid or chlortetracycline but poorly or not at all to vitamin B.12. In our patient (Case 1) evidence of bacterial interference with small intestinal function was obtained by giving aureomycin by mouth when faecal fat loss was reduced to almost half. It seems inescapable that bacterial colonization of parts of the intestine normally sterile is the basic cause of the syndrome, although the exact mechanisms involved are still far from clear (Badenoch, 1958). A change in the bacterial flora might condition vitamin deficiency in the host either by suppression of those organisms which synthesize vitamins or by the overgrowth of others which require the vitamins for their own metabolism. An abnormal bacterial population in the bowel may also be important in producing steatorrhoea, and Frazer (1949) has suggested that bacterial lipolysis of dietary fat may produce irritant fatty acids which are poorly absorbed and cause diarrhoea and the oversecretion of mucus.

Steatorrhoea, when it develops, leads to further nutritional disturbance by the impairment of absorption of fat-soluble vitamins, and this must be accepted as the probable explanation of the osteomalacia observed in our first patient. Certainly the

theory that bacterial overgrowth in stagnant loops of bowel is chiefly responsible for the changes observed in the experimental anaemias in animals and the disease in man accords best with the facts. It seems unlikely that diversion of the intestinal contents *per se* is the sole or even the major cause of the illness in patients with entero-anastomoses. Barium meal examination usually demonstrates the preferential passage of the medium via the normal route; in many cases the fistula cannot be demonstrated by this means and barium enema study is by far the most successful method of diagnosis.

Though absorption can generally be improved with antibiotics and nutrition enhanced with a high-calorie, high-protein, low-fat diet with vitamin and mineral supplements, undoubtedly the treatment of choice in patients with the blind-loop syndrome is the restoration of the normal anatomy of the bowel. This is often impossible in cases where the lesions are multiple but in patients with gastro-colic, duodeno-colic, or jejuno-colic communications, simple repair of the fistula is usually strikingly successful.

Most benign duodeno-colic fistulas have been discovered during the course of investigation of patients with a long history of ill health characterized by diarrhoea and malnutrition. The duration of illness in the reported cases ranged from a few months to 23 years and only four patients gave a short history of acute ill health. Our second patient (Case 2) whose fistula was an almost immediate sequel to the perforation of a post-bulbar duodenal ulcer presented as an acute abdominal emergency. In this case the sequence of perforation, localized abscess formation, and eventual discharge into the colon provided the means of spontaneous cure. Such an event may occur more commonly than is recognized.

The symptoms of benign duodeno-colic fistula have a constancy of pattern which, without being typical, should arouse suspicion of its presence, particularly in patients with a history of duodenal ulceration. The most common symptom is loss of weight; on occasion this may be very great, as in the patient described by Ormandy and Bargen (1939) whose weight fell by 100 lb. Diarrhoea was a feature of all but two of the 14 cases reviewed by Clayton and Thornton (1953); vomiting occurred in seven and was faeculent in two. Clayton and Thornton comment on the surprising fact that only four patients mentioned the passage of undigested food with the stools and it is likely that more examples of malabsorption would be discovered if this possibility were to be borne in mind.

The recognition of benign duodeno-colic fistula is important because the therapeutic dividends are high. Its surgical correction can usually be accomplished quickly and easily and with it the patient is transformed from a state of chronic invalidism to one of full health unless the condition be part of a wider pathological process that requires its own special measures.

Ogilvie (1950) comments that the closure of a benign duodeno-colic fistula gives a surgeon the biggest return in gratitude with the least outlay of time and skill. We concur, and add only that on occasion nature may accomplish the same result.

We should like to thank Professor S. J. Hartfall and Professor J. C. Goligher for permission to publish the details of Case 1. The second patient was under the care of Dr. T. D. Kellock, and to him and to Dr. F. Avery Jones we are grateful for much helpful criticism.

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# SURGERY IN BLEEDING PEPTIC ULCERS*

BY

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*Mansfield*

This paper records a study of 400 patients admitted for haematemesis and melaena. Emergency surgery was undertaken on selected patients but the overall mortality increased when more frequent emergency operations were performed in the latter half of the series.

The proper management of haematemesis and melaena is a constantly recurring problem. Our material consists of 473 patients admitted for haematemesis and melaena between January, 1953, and July, 1958. Four hundred of these (87%) were for proved or suspected peptic ulceration, and the main object of this paper is to discuss the place of surgery in this group. The overall mortality of the ulcer group was 6·25%. Ninety-eight (24·5%) were submitted to emergency surgery. The remaining 73 patients (13%) bled from causes other than ulcer. The Mansfield hospitals serve a population of some 200,000 in a well-defined area. All patients admitted to hospitals and nursing homes for definite haematemesis and melaena are included and classified according to Avery Jones (1956).

## Analysis of Results

In the analysis of results, the ulcer group as a whole is considered first, then all patients in the ulcer series operated on in the acute phase or later. Next comes a summary of other operations done for peptic ulcer over the same period. A more detailed account of the emergency operations (that is within 24 hours of bleeding) in the ulcer group and their results follows. The first 200 and the second 200 of the whole peptic ulcer group are then compared. Finally, there is a short section on the causes of bleeding other than an ulcer, and the emergency operations that were done in this group.

## The Ulcer Group as a Whole

Diagnosis, Mortality, and Extent of Emergency Surgery.—Table I shows how the whole ulcer group divided according to the emergency operations, diagnosis, and mortality. There were 400 admissions and 358 patients. Chronic ulcers (58%) were diagnosed by radiology or at operation. Duodenal ulcers outnumber gastric ulcers by 159 to 70. The acute lesion group (32%) refers to those patients in whom radiology failed to show an ulcer three weeks or so after admission. The unclassified group (6%) refers to incompletely investigated patients with strong presumptive evidence of peptic ulceration. The post-operative group (4%) followed gastro-enterostomy or partial gastrectomy. The whole series mortality is slightly higher for gastric ulcers (10%) than for duodenal ulcers (8·8%), although the operative mortality was rather higher for duodenal ulcers. The acute lesion group had a mortality of 4·2%. No necropsy was done on the patient who died in the unclassified group. None of the post-operative group died.

Table I

DIAGNOSIS, MORTALITY AND EMERGENCY OPERATIONS IN 400 ADMISSIONS FOR BLEEDING PEPTIC ULCER

| Diagnosis | Total | Deaths | Emergency Operations |
|---|---|---|---|
| Duodenal ulcer | 159 | 14 (8·8%) | 45 |
| Gastric ulcer | 70 | 7 (10·0%) | 37 |
| Acute lesion group | 125 | 3 (4·2%) | 13 |
| Unclassified ulcer | 27 | 1 (3·7%) | 0 |
| Post-operative ulcer | 19 | 0 0 | 3 |
| Totals | 400 | 25 (6·25%) | 98 |

Age, Lesions, Mortality, and Sex.—The effect of age on the death rate is shown in Table II.

Table II

MORTALITY BY AGE IN PEPTIC ULCER GROUP

| Age | Number of Cases | Deaths |
|---|---|---|
| 25 | 20 | 0 |
| 25-34 | 32 | 0 |
| 35-44 | 55 | 0 |
| 45-54 | 97 | 3 (3·1%) |
| 55-64 | 96 | 2 (2·1%) |
| 65-74 | 70 | 12 (17·1%) |
| 75-84 | 23 | 7 (30·4%) |
| 85+ | 7 | 1 (14·3%) |
| Totals | 400 | 25 (6·25%) |

* Based on papers read at a meeting of the East Midland Surgical Society held in Mansfield.

Thirty-eight per cent of the patients were over 60. The mortality in patients below 60 for the whole series was 1·2%, and above 60, 14·5%. The three deaths in patients below 60 were all in men, two after emergency operations (one with the dangerous combination of bleeding and perforation), and the other the unclassified death in the medical wards. There were 19 deaths (19%) in the 99 chronic ulcer patients over 60, and eight deaths (37%) in the 30 over 75. The proportion of chronic ulcers increases with age and includes a relative increase in gastric ulcers. The mortality in the chronic ulcer group over 60 is 19·2% and in the other groups 4·8%.

There were nearly twice as many men as women in this series (263 : 137). The mortality in men (7·6%) was more than double that in women (3·6%), in spite of slightly higher age and gastric ulcer incidence in women.

Recurrent Bleeding.—Just over a third of the patients had recurrent bleeding after admission and the mortality rose from 2·3% in the 266 patients who did not have recurrent bleeding to 14·1% in the 134 who did. Chronic gastric ulcers were most prone to bleed again (56%), then chronic duodenal ulcers (38%), post-operative lesions (27%), and last the acute lesion (18%). The mortality of patients over 60 who bled again after admission was 25% for chronic gastric ulcers and 33% for both chronic duodenal ulcers and the acute lesions. Below 60 there was no mortality except in the chronic duodenal ulcer group, where it was 2·3%.

Seasonal Incidence.—Three out of five of the 98 emergency operations were done in the winter months from October to March, although the 400 admissions were divided almost equally between winter and summer months. Cates (1959) found an increase in bleeding in the winter months.

Deaths in Medical Wards.—There were 11 deaths in the medical wards. The youngest, a man of 54 admitted moribund with a haemoglobin of 24%, died unclassified. The other 10 patients were aged between 68 and 89 (average 75). Of these, five died at various stages between being put to bed and the starting of a transfusion. An air embolus was found at necropsy in one who had not been transfused. Four others died after transfusion but within 24 hours of admission. In this latter group who never became fit for surgery was a man who died on his third admission for bleeding. His gastric ulcer had previously perforated. Also in this group was a man who had severe cor pulmonale and died three days after admission.

## All Operations in Bleeding Ulcer Series

Operation before Discharge from Hospital.—Emergency surgery (within 24 hours of bleeding or recurrence of bleeding) was used for 98 patients (24·3% of the admissions) in the ulcer group with mortality of 14·3%. A further small "early elective" group of 12 patients was operated on within a week of bleeding. There were three deaths: a patient of 60 died with cerebral thrombosis, and two others, aged 61 and 70, of pneumonia. Another group of 22 patients was successfully operated upon later and perhaps more wisely before their discharge from hospital. In all nearly a third of the patients admitted with haematemesis and melaena due to suspected or proved peptic ulceration have been operated on before their discharge from hospital.

Emergency Operations.—This group of 98 patients (Table III) includes 55% of the chronic gastric ulcers, 28% of the chronic duodenal ulcers, and 9% of the acute lesion group in the whole series.

Table III
NINETY-EIGHT EMERGENCY OPERATIONS

| Diagnosis | Emergency Operations | |
|---|---|---|
| | No. | Mortality |
| Duodenal ulcers | 45 (28·0%) | 8 (18·0%) |
| Gastric ulcers | 37 (55·0%) | 4 (11·0%) |
| Acute ulcers | 13 (9·0%) | 2 (15·0%) |
| Post-operative ulcers | 3 (19·0%) | 0 (0·0%) |
| Totals | 98 (24·5%) | 14 (14·3%) |

Below 70 years of age the mortality for emergency operations was 6·4% but above 70 it was 43% (Table IV). A third of the series were women, and only two died, aged 72 and 84. The highest mortality group was for men with chronic duodenal ulcers, of whom eight out of 36 (22%) died.

In 95 patients a partial gastrectomy of the Polya type was done for most of the duodenal ulcers, and in a few a Billroth I type of partial gastrectomy was done. A Billroth I operation was done for most of the gastric ulcers with an occasional Polya operation and one wedge resection for the remainder of

Table IV
AGE AND MORTALITY IN EMERGENCY OPERATION FOR ULCER

| Age | Number of Patients | Deaths |
|---|---|---|
| 49 | 21 | 0 |
| 50-59 | 33 | 2 (6·1%) (1 with perforation) |
| 60-69 | 23 | 3 (13·0%) |
| 70-79 | 19 | 8 (42·0%) |
| 80-89 | 2 | 1 (50·0%) |
| Totals | 98 | 14 (14·3%) |

the gastric ulcers. There were two vagotomies with oversewing of the bleeding stomal ulcer, one done successfully by Mr. M. J. Murphy on a man of 84 who had had a previous gastro-enterostomy. The inside of the stomach remnant was always carefully inspected but gastrotomy was not often performed before gastrectomy.

Three surgeons did 89 of these operations, with 12 deaths, and five were concerned in the remaining nine with two deaths.

Of the 98 patients, 88 had had a haematemesis as well as a melaena, and 93 either continued to bleed or had recurrent bleeding after admission. Many of the elderly patients had the usual serious associated lesions found in the literature. In one patient the large inflamed duodenal ulcer could be felt before operation.

CAUSES OF DEATH.—The patients who died received an average of 5 to 6 pints of blood. Post-operative chest complications and leaking suture lines head the causes of death (Table V) after emergency gastrectomy as they do after the elective operation. The leaking duodenal stump occurred in a patient bleeding fast from a large, inaccessible, penetrating duodenal ulcer. He might have been saved by transfixion ligature of the bleeding point, with pyloroplasty and possibly vagotomy. The pancreatitis might perhaps have been avoided in the same way, or by leaving the ulcer and risking the rare chance of a secondary haemorrhage. Patients in the miscellaneous group faded away, one with a possible coronary thrombosis. Another patient had the dangerous combination of haematemesis and perforation. One patient had such a bad chest that his operation was deferred on this account until after his third and fatal recurrent bleed.

TABLE V

CAUSES OF DEATH AFTER EMERGENCY GASTRECTOMY IN 98 CASES

| | |
|---|---|
| Post-operative chest complications (1 after burst abdomen) | 4 |
| Embolus (1 after burst abdomen) | 3 |
| Leaking duodenum | 1 |
| Leaking gastro-duodenal anastomosis | 1 |
| Pancreatitis | 1 |
| Severe wound infection (streptococcal) | 1 |
| Miscellaneous | 3 |

COMPLICATIONS.—Non-fatal complications include a fourth pulmonary embolus, two more burst abdomens, and two leaking suture lines, a high incidence of these three complications. One patient had a discharge through his wound after a Billroth I partial gastrectomy, eventually healing, but needing a further operation months later for pyloric stenosis. The other had one of the curious delayed duodenal stump leaks following Polya gastrectomy eight weeks after he left hospital, and is now well.

PATIENTS WITHOUT CHRONIC ULCER AT LAPAROTOMY.—The 13 patients who did not have a chronic ulcer at laparotomy are of particular interest. All except one, a man of 64 with severe recurrent bleeding, had had a typical ulcer history with a previous admission for bleeding. An ulcer was said to have been found in three of the seven patients who had previously had a barium meal.

At operation, six were found to have an acute ulcer, one acute gastritis, and one hypertrophic gastritis. In the remaining five petechiae and acute erosions were recorded, but no histological abnormality was reported in the three examined. All were treated by partial gastrectomy and so far, a year and a half after the end of the series, none have bled again, or had further dyspepsia.

FURTHER BLEEDING AFTER DISCHARGE.—By the end of the series four of the 84 survivors had already been re-admitted with bleeding and one other had a small bleed at home. Three of the five were men who had had Polya gastrectomies for duodenal ulcers, and are well so far. There were two interesting women with duodenal ulcers and also multiple small bowel haemangiomata. One had had a Billroth I gastrectomy and may have bled the second time from the haemangiomata, but the other developed a stomal ulcer after a Polya gastrectomy and later had a vagotomy. These patients are included in Table III. A fourth patient died from a stomal ulcer as a terminal event after admission for another cause: he had had a leiomyosarcoma of the small bowel resected at the time of the emergency gastrectomy for a bleeding duodenal ulcer.

OPERATION BEFORE END OF SERIES.—A further 24 elective operations were done on a subsequent admission, and nine patients treated medically in this series subsequently had an emergency operation from which two died. A third patient treated medically died later, also from bleeding. He was not fit for operation on his later admission. As far as we know, none of those treated medically perforated after discharge from hospital, although one did perforate in hospital and died after emergency gastrectomy. By the end of the series nearly half of all the patients who survived had been operated on, either at the time of bleeding or later, and as time goes on this proportion will increase. Thus four out of five chronic gastric ulcer patients who survived after admission for bleeding have been operated on, compared with two of three chronic duodenal ulcers. In the post-operative group (Table VI) nine of 16 patients had operations. No

TABLE VI

POST-OPERATIVE GROUP (BLEEDING AFTER PREVIOUS GASTRIC OPERATIONS)

| Previous Operation | Total Number | Operations | | | No Operation |
|---|---|---|---|---|---|
| | | Total | Polya | Vagotomy | |
| Polya for duodenal ulcer | 6 (1)* | 2 | 0 | 2 | 4 |
| Gastroenterostomy | 6 (1) | 4 | 3 | 1 | 2 |
| Billroth for duodenal ulcer | 3 (2) | 2 | 1 | 1 | 1 |
| Billroth for gastric ulcer | 1 (1) | 1 | 1 | 0 | 0 |
| Totals | 16 (5) | 9 | 5 | 4 | 7 |

*No. of women in brackets.

ulcer was seen on the radiograph after barium meals of the seven patients in this group who were not operated upon and they were all well when the series ended.

PEPTIC ULCER SURGERY 1953-58.—During the time covered by these 400 admissions for bleeding with 98 emergency operations, 241 perforated ulcers were dealt with and 510 elective operations for peptic ulcer were performed. Simple suture of the perforation was carried out in most cases, with a mortality of 6%. The mortality of all the elective procedures was 2·4%. These operations were done by consultants and registrars, and nine out of 10 were partial gastrectomies. Vagotomy was becoming more frequent towards the end of the series.

There were three deaths after emergency operations for bleeding ulcer complicating another disease. This group is excluded by definition from the main series.

### COMPARISON OF FIRST AND SECOND PARTS OF SERIES

The first 200 admissions for bleeding peptic ulcers were from January, 1953, to the beginning of February, 1956, and the second 200 followed until July, 1958.

In the first 200 patients there were 34 (17%) emergency operations, with four deaths after operation and five in the medical wards. In the second 200 in the series, there were 64 (32%) emergency operations with 10 deaths after operation and six in the medical wards. The overall increase in the whole series mortality rate was from 4·5% to 8%. The number of patients dying without operation has increased in the second half from five to six and the number operated upon as an emergency has almost doubled, with some increase in the operative mortality.

There was a slight predominance in the number of chronic ulcers in the second series (117 to 112), and in the group over 60 years of age, the number of chronic ulcers was greater in the later series by 56 to 43. Of these patients, 34·5% were over 60 in the first part of the series and 41% were over 60 in the second part. The incidence of recurrent bleeding was also higher in the second series (73 to 61). In the emergency operations there was much the same relative distribution of types of ulcer, including the acute group. The ages were rather higher in the second half of the series.

### CAUSE OF BLEEDING OTHER THAN ULCER

Our present concern in these patients (Table VII) is with diagnosis and not with the details of treatment. Seventy-three of the 473 admissions for haematemesis and melaena were due to causes other than suspected or proved peptic ulcer (Pease, 1959). Two patients with blood diseases also had ulcers but probably bled because of the blood diseases.

TABLE VII

CAUSES OF BLEEDING OTHER THAN ULCER IN 73 ADMISSIONS

| | No. of Admissions |
|---|---|
| Bleeding oesophageal varices | 25 |
| Carcinoma of stomach or oesophagus | 13 |
| Blood diseases | 13 |
| Hiatus hernia | 9 |
| Drugs | 5 |
| Vascular accidents | 3 |
| Uraemia | 2 |
| Diverticulitis | 1 |
| Duodenal polyp | 1 |
| Munchausen syndrome | 1 |
| Total | 73 |

EMERGENCY OPERATIONS FOR BLEEDING NOT DUE TO PEPTIC ULCER.—There were six emergency operations in the 64 patients without ulcers admitted on 73 occasions. One carcinoma of the stomach was resected after bleeding and perforation. The other five patients had cirrhotic livers. Two men also had ulcers demonstrated radiologically, and one had perforated previously. At laparotomy in both cases the bleeding was from the varices and not from the ulcers. Another man who had never vomited passed bright red blood by the rectum and died on the table. A woman had a Billroth I partial gastrectomy on her second admission for bleeding. Previously a duodenal ulcer had been suspected by the radiologist, but at operation there was no ulcer and no enlargement

of the liver or spleen. Two years later, after her third bleed, it was realized that she had portal hypertension. She is now well after a portocaval anastomosis. In retrospect, the fifth patient with cirrhosis should not have been operated on.

Oesophagoscopy had often been done in patients with cirrhosis and the presence of varices did not always exclude an ulcer as a cause of the bleeding. It is not always conclusive, but mistakes usually occur in just those cases in which it is omitted. Patients with bleeding oesophageal varices are usually treated at this hospital in the first instance with a Sengstaken bag.

## General Management

Medical Régime and Indications for Transfusion.—All patients with haematemesis and melaena are admitted in the first instance to the medical firm on duty. A surgeon is informed of all patients over 45 years of age and others with a proved ulcer or recurrent bleeding. For most patients orthodox medical treatment is employed with early feeding, rehydration, and blood transfusion as indicated. Facilities were not available for blood volume studies (Gunz, Gebbie, and Dick, 1954; Tibbs, 1956). Clinical judgment, haemoglobin estimation, and packed cell volumes have been used as the index for transfusion. All patients whose haemoglobin is below 60% are transfused. Careful assessment and continued observation are necessary, particularly in those patients who have bled severely before admission, and those whose blood pressure is low and pulse rate raised at the time of admission. The first pint is usually given in three hours unless the patient is bleeding fast. If the patient's condition is not stable after 3 pints of blood, the surgeon is again consulted. Dunphy (1954) advises surgery if the patient's condition is not stable after 4 pints of blood, and Elliott, Hartle, Marshall, and Zollinger (1958) if not stable after 5 pints of blood.

Stomach aspiration has not been used as a routine except to help in the diagnosis of patients who have only had melaena. Emergency fluoroscopy and endoscopy have not been used, nor has oral adrenaline and stypven (Brandon, 1956).

Most patients recover on this medical régime (75·5% in this whole series). Those who need an elective operation before discharge from hospital (9% of this series) are generally better operated on after full recovery in three weeks' time. Those who do not respond to the medical régime and in whom surgery is indicated are watched carefully, and the decision if and when to operate (24·5% of this series) is made generally in consultation with a consultant anaesthetist.

Indications for Emergency Surgery.—The logical employment of emergency surgery is for those patients who are likely to bleed to death without it. The criteria of selection have varied in this series within the broad principles first suggested by Avery Jones (1947) and amplified by others. The approach has been more aggressive in the second half of our series. Each patient must be judged on his merits, particularly in the older age groups, when severe bleeding is more serious, and there are often other adverse complicating features. These may be an indication for surgery rather than the reverse (Stewart, Cosgriff, and Gray, 1956; Snyder and Berne, 1957). Patients of middle age and above with chronic ulcers tend to bleed again with a worsening prognosis. In our series the mortality was between 25% for chronic gastric ulcers and 33% for chronic duodenal ulcer patients over 60 with recurrent bleeding. Any patient may bleed to death from an acute ulcer, as did one of our patients, or from gastritis. The incidence of bleeding ulcers is less in women than in men, and the mortality in women less than half that of men in our series.

There is general agreement on early operation for concomitant bleeding and perforation and for most patients with chronic gastric ulcers of whom 56% bled again in this series. In patients with chronic duodenal ulcers, Chinn, Littell, Badger, and Beams (1956) found that 31% bled again after admission compared with 38% in this series, and of those who bled a second time 64% bled a third time. Gray, Olson, and Manrique (1957) give even higher figures, and emphasize the danger of one massive bleed in the elderly. Chinn *et al.* (1956) stress the poor prognosis in men over 50 with multiple acute erosions. Weber, Nash, and Gregg (1957) consider that the administration of 10 pints of blood give a patient a bleeding diathesis.

The decision to operate rests on the history, severity or recurrence of bleeding, and the age of the patient. At present our arbitrary age divisions are at 40 and 55. Thus emergency surgery may be employed at once for a patient over 40 with a known gastric ulcer and a severe bleed, and is certainly employed if there is a recurrence of bleeding. In a patient below 40 years one would normally await a recurrence of bleeding. The patient aged over 55 with a known chronic duodenal ulcer would be operated on at once if the bleeding were severe, or if the bleeding were recurrent in a patient over 40 years. Patients with a good clinical history of chronic peptic ulceration are treated in the same way. The benefits of surgery seem to be at least partly responsible for our mortality of 1·7% in patients under 60, and 7·4% in patients under 75, with chronic ulcers. Those with a short or a typical

history are not operated on unless the bleeding is persistent or recurrent. Operation is undertaken earlier in the older age groups, and in all age groups with more severe bleeding. Occasionally an unusual blood group may influence the decision to operate. Once this decision has been made the patient is made fit for surgery as soon as reasonably possible. We have not used arterial transfusion. When there is doubt in the diagnosis, oesophagoscopy is carried out before laparotomy.

## Discussion

The incidence of bleeding varices in Great Britain (5·3% in our series) is generally less than in published series in the U.S.A., where there has been an increasingly aggressive attitude to accurate diagnosis by emergency fluoroscopy and endoscopy (Katz, Friedman, and Selesnick, 1958; Switzer and Nichol, 1958; Warthin, Ross, Baker, and Wissing, 1953; Baker, 1959; Rigler, 1959). The routine use of emergency barium meals would not be practicable in this hospital even if thought desirable. Gastroscopy has not been used in our series. Oesophagoscopy has probably not been used as extensively as it should have been in some doubtful cases.

Some physicians treat patients with bleeding ulcers entirely without surgery. Miller (1954) of Dallas, Texas, has had no deaths in 400 patients treated medically, and Duggan (1956) of Newcastle, New South Wales, has had no patient operated on in the last two years. Much of the controversy about the treatment of the bleeding peptic ulcer is still due to incomplete information. Comparison of series of different ages, types of ulcer, degree of bleeding and so on, can be misleading, and the fate of all patients must be known whether or not they are treated by surgery (Tanner, 1950). Progress after the acute episode must also be considered before a final assessment of mortality.

Most recent authors, however, advocate selective surgery, and it is probably true to say that the whole series mortality of the bleeding peptic ulcer is usually below 10% and an average of 15% have emergency operations. The operative mortality is generally of the order of 15%, and 15% of patients do not have a chronic ulcer although at least half of these may have an acute ulcer or gastritis. The number of acute lesions found at laparotomy will vary with the number of patients operated upon as an emergency.

From the very considerable literature available only some recent large series in the United Kingdom are compared in Table VIII.

Tanner (1950) has several series with a varying incidence of emergency surgery and varying mortality (7·5% to 12%). He has an exceptionally high proportion of old patients with gastric ulcers. His mortality in the Finsterer phase when 59% were operated upon as an emergency was if anything lower than on more conservative régimes. Our mortality increased from 4·5% to 8% as the use of emergency surgery increased from 17·5% to 32%.

The increasing number of yearly admissions from bleeding peptic ulcer, and their increasing ages have been reported by Fraenkel and Truelove (1955), Avery Jones (1956), and Large (1960). Our second series of patients were older, had more chronic ulcers, and more recurrent bleeding. These factors, together with the larger number who have had definitive surgery, may account for the increased mortality. On the other hand, we may well have been doing more emergency surgery than was necessary. Avery Jones (1956) has emphasized the increase in whole series mortality that may occur in these circumstances. In spite of increasing numbers of older patients with more chronic ulcers, the mortality in Oxford fell from 19% to 5·3% (Fraenkel and Truelove, 1955) and in Reading from 7·4% to 5·9% (Large, 1960), while it remained between 7% and 8% at the Central Middlesex Hospital, London (Avery Jones, 1956).

The ages and mortality rate of our patients fall between the extremes in Table VIII. The series with the highest proportion of elderly patients had the highest mortality, as might be expected.

Chesterfield is a neighbouring town to Mansfield with a similar population, but Gaunt (1960), in a

Table VIII

Recent Comparable Series

| | % Patients Over 60 | % Emergency Operations | % Series Mortality |
|---|---|---|---|
| Fraenkel and Truelove (1955) Oxford | 42·0 | 14·1 | 5·6 |
| Waterson (1956) Cambridge | 45·0 | 9·0 | 9·3 |
| Avery Jones (1956) Central Middlesex | 40·0 | 10·0 | 7·9 |
| Cates (1959) Bristol | 33·0 | 13·5 | 5·4 |
| Gaunt (1960) Chesterfield | 34·5 | 4·5 | 4·5 |
| Large (1960) Reading | 50·9 | 19·9 | 5·9 |
| Present series, Mansfield | 38·0 | 24·5 | 6·25 |
| 1953-56, Mansfield | 34·0 | 17·0 | 4·5 |
| 1956-58, Mansfield | 41·0 | 31·0 | 8·0 |

very similar but somewhat younger series, had only 4·5% of his bleeding ulcer patients operated on with a whole series mortality of 4·5%, the same as in the first half of our series, when 17% were operated upon as an emergency.

The number of patients found with a chronic ulcer varies at emergency operation considerably. Spencer and Maloney (1956) reviewed 49 such patients, including 11 of their own. Bruce and Dudley (1959) in their series of some 180 emergency gastrectomies had 31 (17%) patients on whom they carried out a blind gastrectomy. In seven of the 31 there was no abnormality. Large (1960) in 97 emergency operations found 20 acute ulcers, and no abnormality on gastrotomy in another four. In our 98 emergency operations we found 13 patients without a chronic ulcer, six with acute lesions, two with gastritis, and five with no gross abnormality. A definite ulcer was found in all the cases of Fraenkel and Truelove (1955) and Gaunt (1960).

In some of the patients without a chronic ulcer, enlarged nodes or thickening may confirm the diagnosis of an acute ulcer, which may be multiple. Sometimes, however, no ulceration is appreciated until the stomach has been opened before or after resection. Most surgeons prefer a gastric resection or possibly a sleeve resection for acute gastric ulcers. Bohn (1949) and Large (1960) have successfully practised submucosal excision for 23 bleeding acute gastric ulcers since 1946. Avery Jones (1956) suggests that this may be done only in women.

There has been much recent concern about the correct procedure when no ulcer or other abnormality is found, the "*laparotomie blanche*" of the Continental authors (Tanner, 1958; Bruce and Dudley, 1959, 1960, and others). Osborne and Dunphy (1957) have described a most careful routine at laparotomy and insist on a wide gastrotomy, also recomended by Gilchrist and Chunn (1954), Schulenburg, Barnetson, and Jacobs (1956), Spencer and Maloney (1956), Avery Jones (1959). Others inspect the inside of the stomach through a speculum or sigmoidoscope introduced at laparotomy.

Before resection it must be established that bleeding is occurring high in the intestinal tract rather than, for example, from a jejunal haemangioma (Read, 1960). Our patient with the leiomyosarcoma of the small intestine was obviously bleeding from a duodenal ulcer. Many surgeons carry out empiric, blind, or speculative gastrectomy, then inspecting the inside of the stomach remnant carefully. Partial gastrectomy cures most of these patients but not all of them, and in a very few even a total gastrectomy may be needed then or later (Shuttleworth and Hutt, 1958; Castagno and Hardaway, 1958; Palmer, 1959).

We did not encounter the rare eponymous Mallory-Weiss disease or the Zollinger-Ellison or Groenblat-Stranberg syndromes. None of our 13 patients without chronic ulcers bled again, even when followed up from two to seven years. If nothing is done except a laparotomy some two-thirds of the patients will bleed again (Gray, Shands, and Thuringer, 1954; Kirtley, Riddell, and Smith, 1957).

Even after partial gastrectomy a distressingly large number of patients bleed again, five in 84 of the survivors in our series. This was most common in men with a duodenal ulcer, four out of 22 in our series. Donaldson, Handy, and Papper (1958) had similar results, as did Boles, Cassidy, and Jordan (1957) who described the recurrence of bleeding as disappointing and challenging. Mydland, Bartholomew, and Ferris (1956) consider that this bleeding is particularly prone to recur after re-operation for stomal ulceration after gastro-enterostomy. Gilchrist and Chunn (1954) regard patients with acute erosions as particularly likely to bleed again. It has been suggested that vagotomy be added to the partial gastrectomy in these groups. Large (1960) found that most patients who bleed after a partial gastrectomy bleed from acute lesions or gastritis, and not from a true ulcer.

The first stage in the operation for severe bleeding is to stop the bleeding and a simple transfixion ligature has been life saving. Albright and Kerr (1955) and I. S. M. Jones (1960) have advocated a more frequent return to this simple principle. Warthin *et al.* (1953), Smith and Farris (1958), Dorton (1958), and Westland, Movius, and Weinberg (1958) combine this with a vagotomy and pyloroplasty in bleeding duodenal ulcers. This procedure might have saved two of our emergency operation patients. Vagotomy without a direct attack on the ulcer is only used in some of the post-operative group. Partial gastrectomy remains the routine emergency operation for most of our patients.

## Summary

Four hundred patients admitted for bleeding peptic ulcer with a mortality of 6·25% are analysed in detail.

Ninety-eight (24·5%) were treated by emergency operations. The 13 patients who did not have a chronic ulcer included six with acute ulcers and two with gastritis.

In the first 200 patients admitted the mortality was 4·5%, 34·5% of patients were over 60, and the emergency operation rate was 17%. In the second 200 the mortality was 8%, 41% of patients were over 60, and the emergency operation rate was 31%.

The indications for surgery, the operations employed, and their complications and results are discussed.

We are indebted to our colleagues, especially Mr. F. J. Milward and Mr. M. J. Murphy, now of Limerick, also to Dr. H. Patel, Mr. A. Whiteman, the Group Medical Records Officer, and his staff for their great assistance in accumulating the data.

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## *New Methods for Diagnosis and Research*

# WIRELESS TELEMETERING FROM THE DIGESTIVE TRACT

BY

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This paper describes the construction and use of "radio pills" which transmit changes in intraluminar pressure.

Most patients dislike intragastric tubes, whether for tests or treatment, more than any other diagnostic or surgical procedure: this was the general opinion of patients recovering from a gastrectomy at Central Middlesex Hospital. There is no doubt, too, that the nausea and distress caused by the presence of a tube has vitiated a great deal of clinical investigation, since the patient's emotional state is known to exert a profound influence on all aspects of gastrointestinal function. For this reason there is an urgent need for tubeless methods of investigation and also because most of the small and large intestine is inaccessible to tubes for all practical purposes (Rowlands, 1960).

The preliminary publications about the construction of wireless transmitters sufficiently small to be swallowed by a patient (Mackay and Jacobson, 1957; Farrar, Zworykin, and Baum, 1957; von Ardenne and Sprung, 1958) seemed to us to represent a distinct advance in gastrointestinal investigation. We therefore decided to follow this up and were fortunate in obtaining the collaboration of Mr. H. S. Wolff and the Bioengineering Laboratories of the National Institute of Medical Research. Theoretically, a wide variety of physiological parameters can be transmitted by such wireless pills. We decided to start by incorporating transducers for recording pressure and temperature into the pills, because these are the easiest to construct. This project having proved successful, a *p*H-sensitive pill is now being developed, using a glass electrode (Wolff and Russ, 1960).

We have studied the performance of these pills in the gastrointestinal tract during the course of their development. This paper presents our experiences and indicates some of the problems we have encountered in the clinical use of the pills, with special reference to those incorporating a pressure transducer.

### Construction of Pill

In designing the pill, it was felt that the clinical value of this promising technique could only be assessed if pills were freely available and of constant quality and performance. It was therefore decided that only commercially available components should be used so that the pills could be produced by a commercial organization as soon as possible.

The construction of the pills and receivers has been described elsewhere (Rowlands and Wolff, 1960; Wolff and Russ, 1960; McCall, 1960). A typical pill is illustrated in Fig. 1 and a diagrammatic cross section in Fig. 2. One end of the pill housing is formed by a "perspex" diaphragm to which a ferrite disc is attached. When the diaphragm bends, the disc is moved and this changes the inductance and hence the frequency of oscillation. This frequency change is transmitted and picked up by a suitable receiver. The power supply is a cylindrical shaped battery, 7·7 mm. in diameter and 3·4 mm. high, and this determines the overall diameter of the pills at 8·8 mm. The battery life is between 30 and 40 hours. In the earlier pills an inertia-operated mercury switch was used. By shaking the complete pill sharply along its axis in the appropriate direction, the mercury could be moved to the ON or OFF position (Fig. 2). This device proved unsatisfactory because the pill sometimes switched itself off in the act of swallowing, indicating that the diameter of the capillary containing the mercury was critical and very difficult to standardize. A new switch has been devised, consisting of a peg which is pulled out of the pill before use so that two spring wires make contact and switch the pill ON. This has proved very satisfactory. It was found that pills which were perfectly stable in air developed a serious drift

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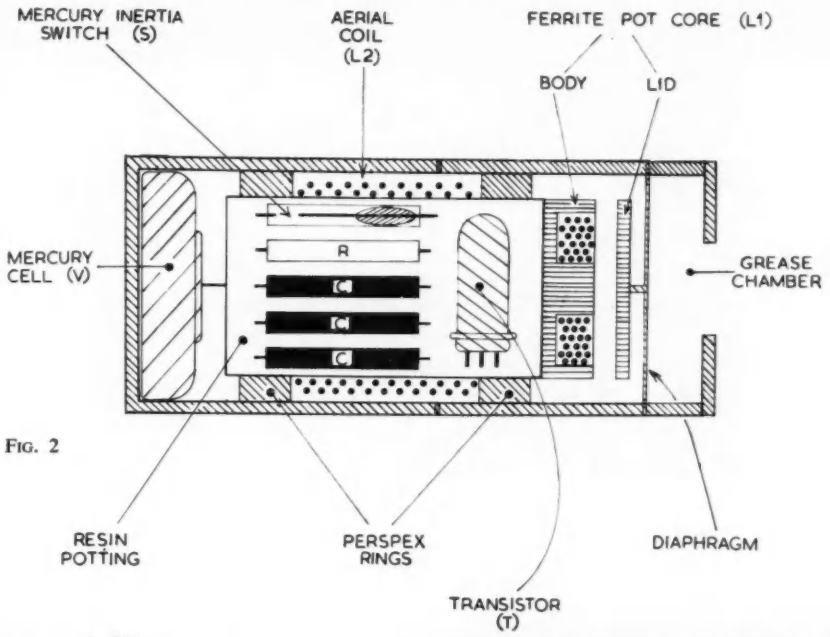



FIG. 2

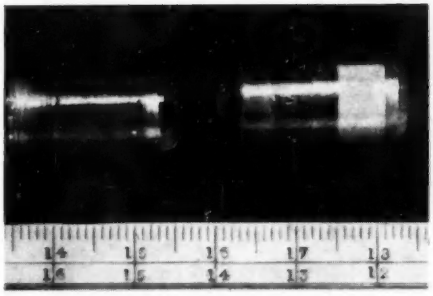


FIG. 1

FIG. 1.—*The pill, that on the right is enclosed in a standard pharmaceutical capsule.*

FIG. 2.—*Diagrammatic cross section of the pill showing constructional details.*

during recordings from the gut. This proved to be due to the effect of fluid acting on the outer surface of the diaphragm, thus causing a small dimensional change. This can be largely prevented by placing a layer of silicone grease in the cup over the diaphragm. The pills are calibrated in water at 37°C. before use and the calibration has been checked in those pills recovered before expiry of the battery.

### TRANSIT TIMES

Thirty-two pills have been swallowed, so far, mostly by normal subjects but a few by patients suffering from gastrointestinal disease. None of our subjects or patients has had any difficulty in swallowing the pills. The transit time through the gastrointestinal tract has varied from 18 hours to four days. The major points of hold-up in normal people are in the pyloric antrum and in the caecum. The factors causing delay in the caecum are not known but the delay at the pylorus appears to be related to the presence of food in the stomach. Although these pills may become sufficiently cheap to be expendable it is a simple matter to recover them if required: the receiving aerial is brought close to the stool and the position of the maximum signal noted. The pill is then directly extracted from this point.

In one patient the pill failed to pass through the gastrointestinal tract. This was a patient in whom a tentative diagnosis of idiopathic steatorrhoea was made on the basis of increased faecal fat excretion, abnormal small bowel enema, delayed xylose excretion, and

FIG. 3.—*Recording intraluminal pressures by wireless on a direct writing recorder.*

abnormal small intestinal biopsy. In this patient the pill passed out of his stomach but failed to progress beyond the left iliac fossa where it remained for three weeks. A repeat small bowel enema was performed which revealed areas of dilatation and multiple strictures of the upper small intestine. At laparotomy, multiple strictures were found in six feet of jejunum and upper ileum resulting from Crohn's disease. The pill was recovered from the resected specimen. While it is not recommended that pills should be given routinely to patients suspected of having intestinal obstruction, in this particular patient the delay in the transit of the pill did speed up further investigation which led to an early laparotomy and resection. Farrar and Bernstein (1958) have reported a similar experience.

### LOCALIZATION OF PILL

One of our main problems has been in localizing the pill after it has passed beyond the ligament of Treitz, despite frequent screening using an image intensifier. For example, in the above patient, the pill appeared to be in the descending colon but the small bowel enema showed that it was actually held up in the jejunum. However, it is sometimes possible to locate the pill approximately from its movement and position on screening. Moreover, we are familiar with the characteristic pressure patterns at different levels throughout the gastrointestinal tract from our previous motility records, using tubes. By correlating these pressure patterns with those transmitted by the pill during its passage through the gut, it has been possible to localize the pill in most cases with a fair degree of accuracy, and with more experience it may be possible to dispense with fluoroscopic control altogether.

### THE PRESSURE RECORDS

Two types of recorder have been used, a direct writing pen recorder (Fig. 3) and a mirror galvanometer. Figures 4 to 8 are illustrative tracings of records obtained at different levels of the gastrointestinal tract.

LOSS OF CONTACT.—In some of the records the trace drops transiently below the base line. This results from loss of contact with the pill when a directional aerial is used. We have observed pills radiologically during a period when contact was being repeatedly lost and noted that this seems to coincide with certain movements of the pill, particularly when it spins on its axis. It does not necessarily imply forward propulsion. This loss of contact has occurred repeatedly in several of our records, especially in the small intestine, but an omnidirectional aerial has recently been devised to overcome this difficulty. However, it may be that some information can be obtained from observation of these periods of loss of contact as they seem to indicate some movement of the pill which may or may not be associated with a rise in intraluminal pressure. For example, it is known that contractions occur in the pyloric antrum at a rate of 3 per minute. When these contractions are powerful, resulting in a rise in intraluminal pressure, the pill is unlikely to spin and a trace as illustrated in Fig. 4 (lower tracing) is obtained. If, however, the contraction rings passing along the antrum are feeble and do not result in a rise in intraluminal pressure, the pill probably rotates and a trace showing loss of contact at a rate of 3 per minute is obtained (Fig. 9). If this interpretation is valid it is possible that more information can be obtained using a combination of a directional and omnidirectional aerial than by an omnidirectional aerial alone.

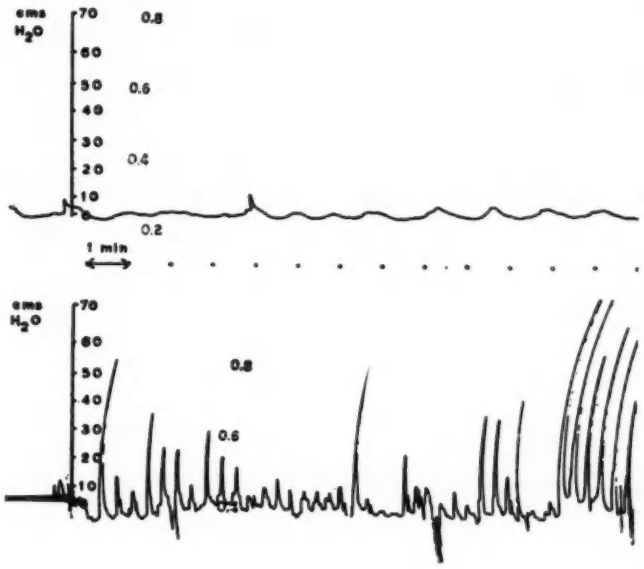



FIG. 4.—*Gastric pressure waves. Upper trace showing gastric tonus activity. Lower trace showing typical 3 per minute antral waves.*

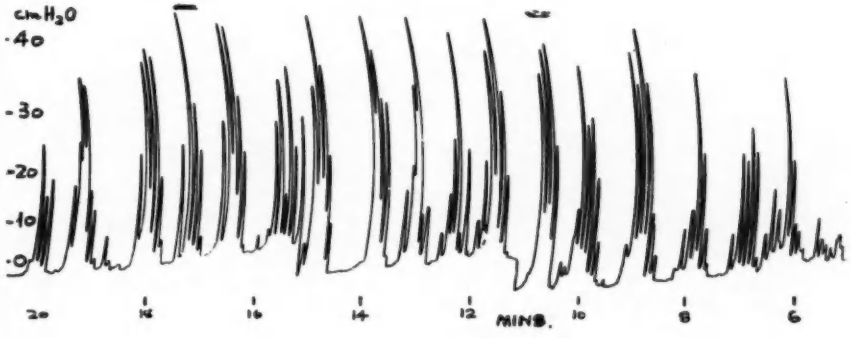



FIG. 5.—*Small intestinal pressure waves (recorded through an ileostomy).*

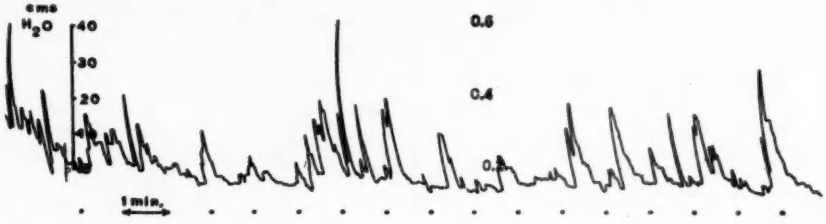



FIG. 6.—*Pressure waves in the area of ileo-caecal valve. On the extreme left is small intestinal activity; on the right caecal activity.*

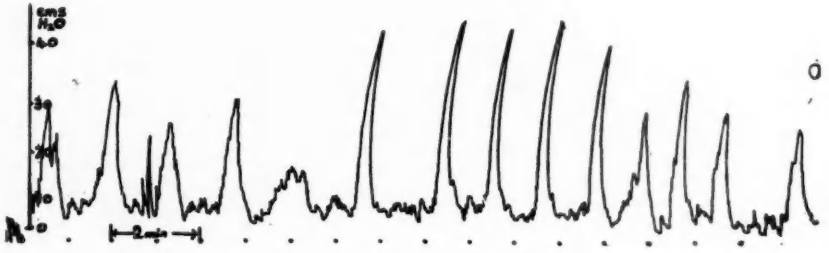



FIG. 7.—*Colonic pressure waves from the region of the splenic flexure.*

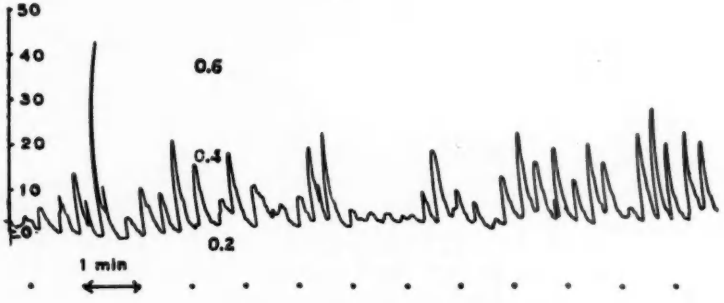
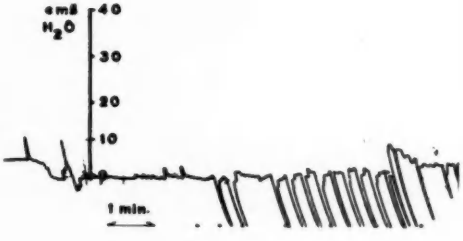



FIG. 8.—*Pressure waves from the pelvic colon.*

FIG. 9.—*Record from the pyloric antrum showing loss of contact with pill at 3 per minute.*



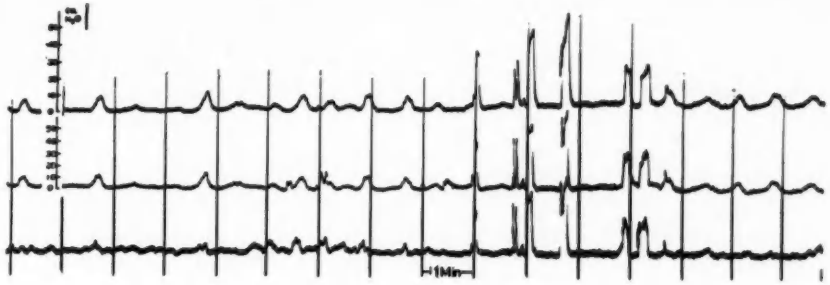



FIG. 10

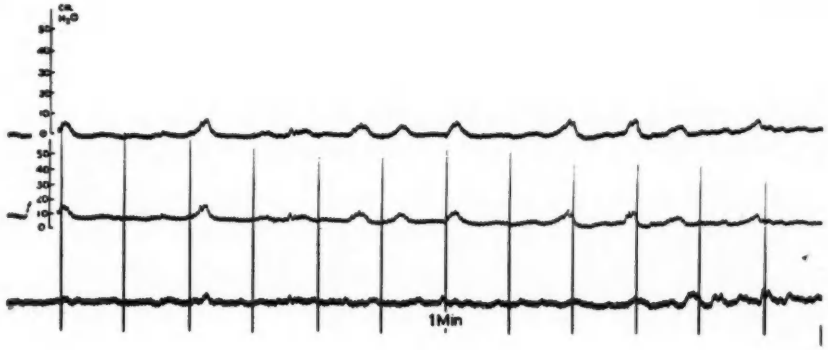



FIG. 11

FIGS. 10 and 11.—*Simultaneous records from a pill and open-ended tube in the same segment of colon. Upper trace, pill record using a mirror galvanometer. Middle trace, open-ended tube record from the same segment. Lower trace, record from miniature balloon 10 cm. distant.*

FIG. 12.—*Simultaneous records from pill and miniature balloon in the same segment of colon. Upper trace, pill record using a mirror galvanometer. Middle trace, miniature balloon recording from the same segment. Lower trace, miniature balloon recording from 10 cm. distant.*

CORRELATION WITH TUBE METHODS.—The records are essentially the same as those we have obtained in the past using open-ended tube and miniature balloon methods from all readily accessible areas of the gut. To confirm this impression it was necessary to obtain simultaneous records with pills and tubes. This could only be done accurately and conveniently by tying the pill to the recording tube and inserting it through an ileostomy or per rectum. It is essential that the diaphragm of the pill is in precisely the same position as the other recording device to ensure that the comparison is made in the same segment of intestine at all times (Connell, 1959). Thirteen studies have been made in this way. There is an exact quantitative and qualitative correlation between the open-ended tube and pill records (Figs. 10 and 11), but there are some minor quantitative differences between balloon and pill records (Fig. 12). However, these occur only when the miniature balloon is subjected to a high squeeze pressure and can be explained by the different dynamics of balloon and diaphragm recordings under these circumstances (Edwards and Rowlands, 1960). Of 100 waves selected at random from the pill tracings, only 19 differed from the corresponding balloon record by more than 33%.

## DISCUSSION

The battery life is usually adequate for recordings from normal subjects but in some patients it has not been long enough for studies of the distal gut. It is possible to prolong the battery life for as much as three weeks (Jacobson, 1960). It is also possible to construct pills which are externally energized, but this introduces other problems and is unlikely to be a satisfactory solution (Farrar, Zworykin, and Berkley, 1960).

Another problem arises from the fact that the reference pressure is that of the air trapped inside the pill body. To allow for changes in atmospheric pressure after manufacture, a small hole is left in the outer case of the pill which is blocked immediately before use. After this has been done, any subsequent changes in barometric pressure will result in errors in the reference pressure, but it is possible to correct these by noting changes in barometric pressure (Jacobson, 1960). In clinical practice this error is unlikely to be important.

A further problem which has not yet been solved is to devise a method for using the pills to record propulsive activity. This can easily be done when tubes are used because three or more recording tips can be used simultaneously. In contrast, it would be difficult to swallow three pills strung like beads on to a short piece of semi-rigid tubing. For this and other reasons we feel that fine tubes will remain the method of choice for studying oesophageal function.

Despite these limitations, there is no doubt that the further development of this tubeless method will result in considerable advances in our knowledge of gastrointestinal function in health and disease. Already, certain new features of gastrointestinal motility have been noted, especially in the previously unexplored areas of the intestine. The method is applicable not only to the study of motility but can be adapted to obtain data about the secretory and absorptive functions of the gastrointestinal tract. These developments present exciting prospects of much new physiological information from an area of the body about which we urgently need new knowledge.

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# HEREDITY IN GASTROENTEROLOGY: A REVIEW

BY

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Attention is drawn to the more important genetic principles which have a bearing on medical problems, and stress is laid on the careful planning necessary if a clinical genetic research project is to produce worthwhile results. There follows a review of the present state of knowledge concerning heredity and various gastroenterological disorders, with suggestions of the lines of research most likely to be rewarding. The view is expressed that the most urgent need is for more knowledge of the genetics of the physiological processes of the gastrointestinal tract.

Physicians have long realized that heredity plays a part in certain conditions. Up to the beginning of this century it was all rather vague, and nothing much could be said other than that in different conditions heredity was either very strong, or only moderately so, or perhaps unimportant. During the past 60 years, however, the study of the mechanisms of heredity, the science of genetics, has made great progress. At first genetics was simple and concerned the effect produced by single genes; applied to medicine it explained the inheritance of many rare diseases which are due to single genes. Gradually it became more complicated and the application of the principles of polygenic inheritance and population genetics began to explain how heredity works in some of the more common conditions. Quite recently the advent of biochemical genetics has uncovered the actual enzymic defect underlying some of the rare single gene diseases, and it may not be long before important advances are made in our understanding of the basic biochemical mechanisms underlying susceptibility to common diseases. Probably the first break through will be in thyroid disorders but diseases of the stomach may not be far behind.

## Genetic Principles Relevant to Medicine

In this section attention will be drawn to the more important genetic principles concerned with disease and some clinical research techniques and their pitfalls will be described. For more detailed descriptions of these subjects there are available three excellent works (Roberts, 1959a; Childs and Sidbury, 1957; Graham and Lilienfeld, 1958).

Gene Action.—Even though the theory of one gene one enzyme is a good working hypothesis and the presence or absence of some genes can be detected by the presence or absence of some chemical substance such as the different haemoglobins or blood group antigens, it must be realized that most genes do not manifest themselves so specifically. Their actions can be modified by numerous factors so that their end-results are variable and lacking in strict specificity (see polyposis). These modifying factors may be environmental or may be other genes, and because of them there may be considerable differences in the clinical picture in different families or even within a family.

A gene may be responsible for an enzyme which is concerned in several metabolic processes and it can, therefore, produce manifold effects. Thus many syndromes affecting several systems of the body have been found to be caused by one gene, for example, galactosaemia with mental deficiency, cataract, hepatomegaly, and jaundice. On the other hand, clinically similar effects can be caused by different genes (see glycogen storage diseas)e.

Another point which must be borne in mind is that environmental influences may simulate the action of genes and produce results (phenocopies) comparable with those effected by genes. This leads to the possibility that amongst the patients with a particular disease there may be some cases genetically determined and others environmental in origin (see pyloric stenosis in infancy). Consequently, genetic entities and clinical entities must be clearly differentiated. A clinical entity or phenotype is arrived at by examining the individual, but a genetic entity or genotype can only be established by a family study.

Single Gene Inheritance.—Most conditions which are inherited in a dominant manner are either trivial or without effect on the reproductive rate, or

else they are exceedingly rare. Recessive conditions are usually much more severe and may even be lethal in childhood, the gene being transmitted from generation to generation by the unaffected heterozygotes. In addition, recessive conditions can be relatively common; if the heterozygotes have some selective advantage over both types of homozygote, the gene can reach a high frequency in the population. The best worked out example of this state of affairs in Man is that of the haemoglobin S gene which in certain parts of Africa results in 7 to 8% of children born being affected by the fatal sickle-cell anaemia. The term "polymorphism" is used when two or more forms exist in a population at frequencies above that which could be maintained by recurrent mutation, and the principles underlying balanced polymorphism and natural selection in general are probably of great importance in resistance and susceptibility to disease. This subject will be mentioned again when dealing with the inheritance of fibrocystic disease of the pancreas.

It is becoming more and more apparent that at many genetic loci of Man, the characters determined by the different forms of the gene, the alleles, are neither dominant nor recessive to one another, or at least that dominance and recessiveness are not absolute. Often in the heterozygote both of the alleles are producing an effect, and in double dose in the homozygote an allele has double the effect. When studying a recessive condition in a family it may, therefore, be worth while examining the unaffected relatives very carefully to see if they fall into two classes for some morphological or biochemical trait. If they do, and in a ratio of 2 : 1, that trait may be the single dose expression of the allele which causes the condition when in double dose (see fibrocystic disease of the pancreas).

The genetic terms "expression" and "penetrance" are often used rather loosely in medical papers. It would seem best to reserve the term expression for variability of manifestation, and penetrance for whether or not anything abnormal can be detected. Thus to state that a gene has variability of expression or incomplete expression would mean that its presence in an individual can always be detected but the clinical picture may be incomplete or variable. A gene with incomplete penetrance, on the other hand, could occasionally have no obvious effect whatsoever, and thus, in a pedigree a generation could be unaffected. It is with these meanings that the terms will be used in this paper. Variability of age of onset, like expression and penetrance, is usually due to differences in the environment or to other genes; only if the age of onset falls into two distinct groups is it likely to be determined by single and double doses of the gene.

POLYGENIC INHERITANCE.—In none of the common diseases of Man in which heredity seems to play a part is the pattern of inheritance clear cut. They tend to occur more commonly in some families than others, but many cases occur quite sporadically with no family history and, even when there is a strong family history, the distribution is not of simple mendelian type. The reason for this is that not only are environmental influences important, but that several genes located on different parts of the chromosomes are involved: their inheritance is "polygenic".

One may ask: "What is the difference between polygenic inheritance and inheritance by single genes which are very subject to the influence of other modifying genes?" The difference is only one of degree and there is probably no clear-cut dividing line between the two types of mechanism. The writer prefers to use the term polygenic for both types and, in a polygenic system, would describe as a "major" gene any gene which is of great importance in determining the presence or absence of the condition, and, for instance, regards susceptibility to duodenal ulcer as polygenically inherited, probably with several major genes. On much the same evidence, however, Pisot, Dubarry, and Duhamel (1957) regard the inheritance as recessive, involving two pairs of genes, with constitutional and environmental factors modifying the manifestation of the disease. The difference between the two interpretations may only appear semantic, but it implies a different approach to the subject of further research and the importance of identifying the various major and minor genes involved.

Polygenic inheritance is the basis of the inherited element in most normal human characters. When several genetic loci are involved in a character one does not find the clear-cut differences found with single gene inheritance. For instance, with height, which is polygenically determined, a population is found to contain a whole range of heights: it is a graded character with a normal distribution curve tailing off to very small people at one end and very tall at the other, but where one draws the limits of normal is rather arbitrary. Since some common diseases have polygenic inheritance, one might expect them also to be graded characters with no clear-cut dividing line between health and disease. This is obviously not so in the case of cancers in which there must be a critical point, but it may be so in conditions such as duodenal ulcer.

To revert to the illustration of the inheritance of height, the offspring of two tall people will tend to be tall and those of two short people to be short. Since many genetic loci are involved it is quite possible for a short person to have a number of

genes which tend to make him tall but which are swamped by a larger number of genes tending to shortness. The offspring of two such short people would, in fact, on the whole be short, but an occasional one might receive all the tall genes from each parent and be a tall person. Applying this to medicine, one can see that with polygenic inheritance it would be quite possible for a disease to occur in someone with no family history of the condition, even though that disease is wholly genetically determined and quite independent of environmental influences. In practice, however, one should not separate the action of genes from the environment, and a disease can be expected to result from both genetic and environmental influences. The relative size of the genetic and environmental components would vary from case to case, and a few cases might be wholly genetic and a few almost entirely environmental.

## Clinical Genetic Research Techniques

There are three types of technique available to study whether or not heredity is involved in the aetiology of a disease. They are all fraught with possibilities for the introduction of bias and inaccuracy, and results have to be examined most critically before being accepted at their face value. Before undertaking clinical genetic research, physicians would be well advised to study this aspect of the subject thoroughly, and also seek the advice of an expert in the field.

Twin Study.—The theory underlying twin studies is that if the concordance ratio is higher for monozygotic than for dizygotic twins, a genetic factor is operating. In general this is probably so, though occasionally a higher concordance rate in monozygotic twins may be due to their having a more uniform environment than dizygotic twins. There are, however, more important reasons why papers giving twin analysis may be misleading; for instance, there are the inaccuracies involved in deciding the zygosity of twins, and the possibility that there is a third type, the product of one ovum and two sperms (Platt, 1956). In addition authors often survey the literature in order to get large enough numbers for analysis and it is possible that cases of concordance among "identical" twins are reported more readily than concordance in "non-identical" twins. The ascertainment of the twins by selecting pairs one of whom is ill is also liable to lead to bias. Harvald and Hauge (1956) are using a technique which should avoid the biases inherent in most other twin studies: they are following up a sample of *all* the twins born in Denmark between 1870 and 1910.

Pedigree Study.—The investigation of the presence or absence of disease over two or three generations of one or a small series of families is of value if the disease is rare, even though information obtained from family members is often inaccurate and may be biased. With common diseases, however, this technique is rarely of value as occasional familial aggregations can be expected by chance alone, and of course, may be the result of non-genetic environmental factors.

Statistical Study.—This involves studying the frequency of a disease in relatives of people with the disease and comparing with the frequency in relatives of people who do not have the disease, or comparing with the morbidity or mortality frequencies of the general population. There may be difficulty in eliminating bias from the selection of patients for study, and there is the problem of incomplete ascertainment, quite apart from the inaccuracies and bias of diagnosis based on the recollection of other family members; it is reasonable to suppose that individuals with a disease are more likely to know about relatives having the same disease than are unaffected individuals. The main trouble with this technique, however, is with the controls which are often not matched for age, sex, race, and socio-economic status. A general population control may be unsuitable as the relatives of patients from a few hospitals may not be representative of an entire country. A solution to these problems may be prospective surveys, in which relatives of patients and suitable controls are followed up each year. The advantages of prospective surveys in eliminating biases have been shown in other fields to outweigh their difficulty, as for example, in the problem of maternal rubella and congenital defects (Hill, Doll, Galloway, and Hughes, 1958).

Interpretation of Results.—Having definitely established that there is a familial aggregation of a disease, it remains to determine whether it is the result of genetic or environmental factors. This problem will remain difficult as long as the environmental factors in a disease are still completely unknown. Some information can be gained from study of spouses of patients; they share some of the environment but are genetically different from the patient, and, if they have consistently lower frequencies than the relatives, it would provide support for a genetic cause. The interpretation of spouse data is rendered difficult by the fact that mating is not random in human populations. Mating within social, economic, racial, and religious strata (assortative mating) has effects which cannot be accurately measured.

When some environmental factors are known, or even are known not to be of importance, the

distribution of the affected relatives in different generations may provide the answer. For instance, Doll and Kellock (1951), working on duodenal ulcer, a condition known to be independent of social class and occupation, found nearly three times the expected incidence in the fathers. They found it difficult to believe that the fathers had been equally subject to the same adverse influences in their childhood as their children were a generation later, and thought there was little room for doubt that genetic factors were responsible for the increased family incidence. In some cases useful information can be obtained from family data without controls; the study of the incidence of a condition in sibships, divided into those with both parents, one parent, or neither parent affected, can give a clue to the mode of inheritance if a major gene is operating.

IDENTIFYING THE GENES CONCERNED.—If the pattern of inheritance is in keeping with a single gene effect, a biochemical study is indicated. With polygenic inheritance a biochemical approach may also be rewarding, but the biochemical defect also is likely to be polygenically controlled and no clear-cut differences between affected and unaffected would then be found.

Apart from the genes determining rare enzymic defects there are very few commonly occurring genes of which the presence can be detected. It is perhaps remarkable that any of them have been found to be involved in disease, but the ABO blood group genes and the genes controlling secretion of the ABO blood group substances in saliva and gastric juice have been shown to be involved in gastro-intestinal diseases (Roberts, 1959b), and the genes which determine the ability to taste phenylthiocarbamide in thyroid disease (Kitchin, Howel-Evans, Clarke, McConnell, and Sheppard, 1959).

A great many diseases have been studied for a possible relationship with the ABO blood groups, but, with the possible exception of rheumatic fever and carcinoma of the uterus, none has been found and confirmed in any condition outside the alimentary tract. In addition to the established relationships with duodenal and gastric ulcer, carcinoma of the stomach and pernicious anaemia, abnormal blood group frequencies have been found in cirrhosis of the liver, diabetes mellitus, mixed parotid tumour, carcinoma of oesophagus, carcinoma of pancreas, and cholelithiasis. Further studies are needed before it can be decided whether or not these are due to chance.

## HEREDITY AND PARTICULAR DISEASES

Some of the conditions which will be dealt with are not diseases solely of the gastro-intestinal tract, but they can all cause lesions in the tract. The amount of space given to a condition will depend, not so much on its frequency and importance, but rather on the degree of uncertainty or the amount of work which has been carried out or on its promise as a subject for further research. The genetic basis of susceptibility to bacterial or parasitic diseases is too large and rapidly expanding a subject for this review. Similarly the collagen diseases affecting the tract are not discussed.

To give all the references to each condition would require too much space, and those given are the most recent reports in readily accessible journals which contain a good bibliography. They are not necessarily the best or fullest articles on the subject. Occasionally, where there has been an outstandingly good article in the past and subsequent work has not added anything of importance, the older reference is given.

Before proceeding it is worth stressing again that these diseases are clinical entities and not necessarily genetic entities. Even in those conditions stated to be due to a single gene, it should not be assumed that all cases of one of them are due to the same gene. As biochemical genetic research progresses it is being shown again and again that a deficiency of any one of several enzymes can lead to the same clinical entity (see glycogen storage disease).

APHTHOUS ULCER.—The familial incidence of this extremely common condition has been investigated without an answer to the problem of whether or not heredity is concerned in its aetiology. Sircus, Church, and Kelleher (1957) found a positive family history in nearly half of their 120 patients, but only 15% had sibs affected. The general population frequency was estimated to be about 20%. On the other hand only 4·1% of the spouses were affected. Farmer (1958) found a positive family history in 39% of 121 patients and the spouse was affected in 18% of the 62 married patients.

APPENDICITIS.—Although family aggregations of appendicectomy have been noted from time to time, there does not appear to have been any statistical study made. As appendicitis may well be more common in particular types of appendix, it would not be surprising if, in fact, hereditary factors are involved. That the anatomy of the organ may be genetically determined is suggested by the report by Downs (1942) of 16 appendicectomies in 22 closely related individuals. In all those operated on there was a band of fibrous tissue binding the appendix to the outer side of the caecum and causing sharp kinking at the base of the organ with constriction of the lumen.

CARCINOMA OF COLON.—The cases of colonic carcinoma occurring in pre-existing familial polyposis are largely determined by the presence of single genes with only slight environmental influence (see polyposis of the intestines). There seems, also, to be a hereditary influence in cases occurring not in association with polyposis, and it is almost certainly polygenic (see Woolf, 1958). In at least one family there may be a major gene without whose presence the disease will not develop. Thus Richards and Woolf (1956) described a family in which 50% of one generation had small adenomatous polyps of the rectum and recto-sigmoid, of similar character, age, and sex distribution to those found in other reported studies of solitary polyps of the colon. There appeared to be a form of dominant inheritance of these polyps, and a relationship between them and the high incidence of carcinoma in the previous generation of this family.

CARCINOMA OF OESOPHAGUS.—This is one of the cancers which has been well studied from the point of view of heredity (Mosbech and Videbaek, 1955), and no evidence was found of any familial tendency. It is, therefore, remarkable that it has been shown that its development can be determined by the presence of a single gene. When Clarke and McConnell (1954) reported a family in which six members had died of oesophageal cancer and postulated a dominant form of inheritance, it is understandable that Steiner (1956) thought the finding was due to chance. Further investigation, however, brought to light an additional family with 12 cases of carcinoma of the oesophagus, and the observation that the cancer developed only in those members of the families who had tylosis (hyperkeratosis palmaris et plantaris). In fact it was calculated that 95% of the tylotics developed the cancer before the age of 65. Tylosis is due to a single gene and there is no doubt that in these families (which are probably related) an unusual and perhaps unique tylosis gene has been responsible for the oesophageal cancer (Howel-Evans, McConnell, Clarke, and Sheppard, 1958).

In the introductory section of this review it was emphasized that environmental factors can mimic a genetic disease. This is an example of a gene mimicking an environmental disease, The tumours in these families were quite indistinguishable clinically and histologically from the usual sporadic oesophageal cancers.

CARCINOMA OF STOMACH.—A great many papers have been published on the role of heredity in gastric cancer, and Graham and Lilienfeld (1958) have made an excellent appraisal of them. In spite of the limitations in the various investigations, the results all tend in the same direction, and suggest that the disease is concentrated in some families more than in others. That this familial tendency is not wholly environmental, but at least partly genetic, is demonstrated by the finding that people of blood group A are about 20% more liable than those of groups O, B, and AB (Roberts, 1957). There is as yet no evidence that the secretor genes are concerned in carcinoma of stomach (McConnell, 1959). The association with pernicious anaemia is further evidence of a genetic effect as there is a strong genetic element in pernicious anaemia.

CHOLELITHIASIS.—A hereditary pre-disposition to gall-stones has been postulated for a long time; Littler and Ellis (1952) found a family incidence of 20%, but the condition is so often symptomless it is difficult to estimate the incidence in the general population. Strong support for a genetic hypothesis has come from twin studies (see Doig, 1957b). The hereditary component is almost certainly not a single gene, but related to cholesterol metabolism which is probabiy controlled by many genes. One of the genetic loci concerned may be the ABO blood group locus, as Kjølbye and Nielsen (1959) have found an increased frequency of group A in 1,369 patients with gall-stones, suggesting that group A people are about 18% more liable than group O people (see also pancreatitis).

COELIAC DISEASE.—Three systematic studies of the inheritance of coeliac disease have been carried out and each has found affected relatives at a much higher frequency than would be expected from estimates of the frequency of the disease in the general population. It is unlikely that the family concentration is due simply to a common environment as parents were found to have been affected in their childhood.

The absence of any clear-cut mendelian pattern of inheritance suggests that coeliac disease is not caused by the lack of a single enzyme. It is more likely that there is a polygenic predisposition to the development of the intolerance to gluten (see Carter, Sheldon, and Walker, 1959).

CONGENITAL ABNORMALITIES.—The present evidence is in favour of the view that the genetic basis of abnormalities present at the time of birth is much the same as that of diseases developing in later life. Some are due to single gene defects, some have polygenic inheritance, and most of them are the result of both environmental and genetic factors. Rubella in the early weeks of pregnancy is still the only environmental cause of congenital defect which has been definitely established, though maternal age is probably a factor. Even so, the results of genetic

research in many of the commoner congenital abnormalities suggest that, even though heredity is involved, it is unlikely to account for all the cases. For instance, Hirschsprung's disease has been reported several times to have a familial tendency. Bodian, Carter, and Ward (1951) investigated the families of 37 index cases and found four of 37 brothers were affected and none of 28 sisters. This frequency is so much higher than the estimated population frequency of 1 in 50,000-100,000 that it must be concluded that genetic factors play some part in the development of the disease. The inheritance is unlikely to be due to a single gene and is probably polygenic. Alternatively it may be that some cases are genetic and others environmental, and a study of the offspring of patients may be as helpful as it has been with infantile pyloric stenosis (see pyloric stenosis in infancy). The report by Boggs and Kidd (1958) of a brother and sister who had no ganglia or nerves from the duodeno-jejunal junction to the anus may have a bearing on the subject.

Two other congenital abnormalities of the gastrointestinal tract have been reported as occurring in more than one member of a sibship. They are so rare that it is unlikely that more than one case would occur in a family by chance or environmental factors alone, and a genetic basis seems likely. They are congenital atresia of the oesophagus (Sloan and Haight, 1956) and tracheoesophageal fistula (Hausmann, Close, and Williams, 1957).

CONNECTIVE TISSUE DISORDERS.—Two hereditary disorders of connective tissue may lead to gastrointestinal bleeding (see McKusick, 1960). The Ehlers-Danlos syndrome is inherited as an autosomal dominant, *i.e.*, the gene is not located on the X or Y sex chromosomes, but is in one of the other 22 pairs of chromosomes, the autosomes. Pseudoxanthoma elasticum (the Gronblad-Strandberg syndrome) is inherited as a recessive, though the typical retinal changes may be found in the heterozygotes.

Berlyne and Platt (1960) have drawn attention to the fact that in most recorded families with pseudoxanthoma elasticum the affected have either been all males or all females. This raises the possibility of partial sex linkage, the locus being on the part of the X chromosome which pairs with the Y chromosome. If this were proven it would be the first demonstration in the human sex chromosomes of crossing-over (the exchange of nuclear material by the X and Y chromosomes), a process which many geneticists think does not take place.

CROHN'S DISEASE.—The occurrence of more than one case of regional ileitis in a family has been reported in about 30 instances. Whether or not the disease is sufficiently common for this to be due to chance is uncertain. Certainly there does not seem to be a strong hereditary tendency. More remarkable than the slight familial aggregation of this disease, however, is its association with ulcerative colitis within families. This may be due to cases of Crohn's disease of the colon being misdiagnosed as ulcerative colitis (Lockhart-Mummery and Morson, 1960), but if the diagnoses are accepted it suggests the possibility that the two clinical entities may have a common basis (see Houghton and Naish, 1958). As both conditions are probably heterogeneous it may be that within them there is a single condition with quite a strong genetic basis. Further progress will probably have to await improved clinicopathological subdivision of both diseases, though a detailed study of the features of the disease in the families in which they both occur might be revealing.

DUODENAL ULCER.—Of the common non-infective diseases of Man, duodenal ulcer has been the most successfully investigated from the genetic point of view. Twin studies led to the conclusion that there may be an inherited basis of the condition (Doig, 1957a), and an excellent statistical survey (Doll and Kellock, 1951) left little doubt that the family aggregations are, in fact, due to a genetic component and not to the members of families having a common environment. (More detailed comments on the genetic basis of duodenal ulcer will be found in the sections entitled "Polygenic Inheritance", "Interpretation of Results", and "Gastric Ulcer".) In such a common condition the study of individual families, because they have a high concentration of the disease, does not contribute to answering whether or not genetic factors are involved; after a genetic basis has been confirmed, however, such families can be supposed to have a large number of the genes underlying susceptibility and might be suitable for more detailed investigation to try to uncover the actual genes concerned and their mode of action.

Confirmation that there is a genetic basis, and that the inheritance is polygenic has come from the demonstration of two of the genetic loci concerned. These are the ABO blood group locus and the locus which determines whether or not the ABO antigens are secreted in saliva and gastric juice. Group O people are about 40% more liable than are those of groups A, B, or AB, and non-secretors are nearly 50% more liable than secretors (Roberts, 1957). If the characters are considered together it is found that people who are both group O and non-secretor are about two-and-a-half times more liable than the least susceptible people, the secretors of groups A, B, and AB (Clarke, Evans, McConnell, and Sheppard, 1959). The O gene and the non-secretor gene

seem to work independently, as, even amongst non-secretors, group O people are significantly more liable than those of the other blood groups (McConnell, 1960).

The mechanism by which these blood group genes influence susceptibility to duodenal ulcer is not yet known. The fact that they are also concerned in carcinoma of the stomach and pernicious anaemia suggest that they play a part in the physiology of the upper gastrointestinal tract as well as in its pathology. Knowledge of gastric physiology, apart from the mechanisms controlling acid production, is still too scanty for any conclusions to be drawn regarding the probable function of the high concentrations of blood group antigens in gastric juice. It may be that their action has an immunological basis, or possibly the blood group genes are pleotropic and concerned in a biochemical process unconnected with the production of antigens. A clue to the mode of action might be found if more was known of the environmental conditions causing duodenal ulcer. Conversely, discovering the mode of action of the antigens should reveal the important environmental factors.

How many other genetic loci are concerned in the genetic basis of duodenal ulcer is uncertain, but it would be reasonable to suppose that genes determining differences in anatomy and, perhaps, differences in personality, may be playing a part. Some idea of the size of the blood group contribution can be given by the data which mean that, if it were not for the non-secretor and O genes, that is, if the whole population were secretors of groups A, B, and AB, there would be 20% fewer ulcers in England. This does not imply that 20% of all ulcers are caused by these genes without the aid of the environment. Environmental factors must be of supreme importance in the overall incidence in the population, and be responsible for the remarkable increase in the past 100 years, as the genes in the population cannot have changed appreciably during that time. If two populations are under similar environmental stress, however, that with the higher proportion of group O people should have a higher incidence of duodenal ulcer. The data from Great Britain suggest that this may indeed be so, the further north the higher the proportion of group O people and probably also the higher the incidence of duodenal ulcer. The genetic implications of the work on duodenal ulcer and islet-cell tumours of the pancreas are at present uncertain, but will be discussed under that heading.

FIBROCYSTIC DISEASE OF THE PANCREAS (MUCOVISCIDOSIS).—In children it is probable that this condition is always inherited as an autosomal recessive trait, and caused by the same gene in double dose. The possibility of several different genes being able to cause the disease has not been ruled out, but the variable clinical picture is more likely to be due to the single gene being modified in its expression by other genes and by the environment (see Smoller and Hsia, 1959). The relationship of adult mucoviscidosis to the formerly fatal disease of childhood is still uncertain both from the clinical and genetic points of view.

It is because the disease was so often fatal before reproductive age and yet it is so frequent in the population (most estimates being about 1 : 1,500 of all life births) that its genetic basis has been of particular interest. If all cases are, in fact, due to the same gene, the frequency of this gene in the population must be about 3%, much too high a level for it to have reached unless it has conferred some selective advantage on its bearers. Since those who were homozygous for it died before reproduction, the advantage must have been, and may still be, enjoyed by the heterozygotes, the 6% of the population who carry one dose of the gene. There is probably a state of genetic polymorphism similar to that of the haemoglobin S gene in Africa; whilst the advantage of one dose of the HbS gene is known to be a degree of resistance to malaria, the advantage of one fibrocystic gene is not known. If further work on the detection of the heterozygote carriers by tests of the electrolyte content of sweat results in a reliable method which can be applied to large numbers of people, it will then be possible to investigate for this hypothetical advantage. Until it is known it will be impossible to assess whether or not the community as a whole is going to benefit from the rise in the gene frequency which will follow the successful treatment of children with fibrocystic disease so that they live and reproduce.

Very little is known of the actual grouping of the genes on human chromosomes, but the gene for ovalocytosis is on the same chromosomes as the Rh blood group locus, and there is also genetic linkage between the nail-patella syndrome and the ABO blood group locus. The possibility that the gene for fibrocystic disease may be linked with the MN blood group locus has been studied by Steinberg and Morton (1956). Confirmation or denial of this will become much easier when the heterozygote carriers of the gene can be scored.

GASTRIC ULCER.—The present position regarding the genetics of gastric ulcer is rather confused, possibly because the disease may not be as distinct a clinical or genetic entity as is duodenal ulcer. Doll and Kellock (1951) showed that duodenal and gastric ulcers tend to be inherited independently and,

at least in clinical genetic research, the two types of ulcer should not be considered together as "peptic ulcer". Taking all gastric ulcers together there is an increased incidence of blood group O, not as marked as in duodenal ulcer, but implying an increased risk in group O people of about 20% (Roberts, 1957). There have been a number of reports of a relationship between group O and ulcer of particular parts of the stomach, but no conclusion can be drawn from them at present (Doll, Swynnerton, and Newell, 1960). The secretor frequency has been tested in only one small series (McConnell, 1960) and, though it does not differ significantly from controls, it may be that non-secretors have some increased risk, though again not nearly so marked as for duodenal ulcer.

GLYCOGEN STORAGE DISEASE.—Hepatomegaly, due to the deposition of excessive amounts of glycogen, has now been shown to be due to defects in at least three enzymes, namely, glucose-6-phosphatase in Von Gierke's disease (liver and kidney), amylo-1 : 6-glucosidase in glycogen disease of liver and muscle, and amyl-1 : 4 → 1: 6-transglucosidase in glycogenosis with hepatic cirrhosis. Enzymic studies have so far failed to reveal the nature of the underlying abnormality in glycogen disease of the heart (see Harris, 1959).

Von Gierke's disease is inherited as a simple autosomal recessive, and the heterozygote carriers of the gene can be detected by elevated glucose-6-phosphate and fructose-6-phosphate levels in the red cells. It is possible that some cases of "familial hepatic cirrhosis" may in reality be examples of glycogenosis with hepatic cirrhosis (Andersen, 1956).

HAEMOCHROMATOSIS.—The occurrence of the complete clinical picture of haemochromatosis in more than one member of the same family is not common, but it occurs sufficiently frequently to suggest that there is a genetic basis to the disease. It is found in sibs and in parent and child combinations.

Studies of plasma iron levels in the relatives of patients suggest that the underlying biochemical defect, the increased rate of iron absorption, may be determined by a single dominant gene; thus half the adult male relatives have an anomaly of iron metabolism.

Various external factors may be important in precipitating clinical symptoms and influencing the severity of the disorder. The most obvious of these is menstruation which can account for the disease occurring almost exclusively in males even though the gene is probably on one of the autosomes and not on the sex chromosomes.

The juvenile type of haemochromatosis, in which both males and females are affected equally, may be due to two doses of the same gene which causes the more frequently seen disease of late onset (see Debré, Dreyfus, Frézal, Labie, Lamy, Maroteaux, Schapira, and Schapira, 1958; Pirart and Gatez, 1958).

HEPATIC CIRRHOSIS.—There do not appear to have been any studies made of a possible genetic component of the susceptibility of the liver to alcohol and other environmental hazards. Familial hepatic cirrhosis is usually inherited as a recessive character, and is probably heterogeneous in aetiology. In some families it is associated with abnormal glycogen storage (Andersen, 1956), whilst in others there may be an upset of amino-acid metabolism (Still, 1955).

In primary biliary cirrhosis no familial aggregation has been noted, but the disease is still of uncertain aetiology; Sherlock (1959) speculates on the possibility that it may be a sensitivity reaction to some drug or a hormone produced at the menopause. She points out that the sensitivity of certain persons to this type of reaction might, as with other sensitivities, be genetically determined.

HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE).—This inborn error of metabolism, which is inherited as a recessive (see Bearn, 1953), has been the subject of much biochemical study. The particular enzymic defect has not yet been identified but it seems that the serum copper/caeruloplasmin copper ratio may be of primary importance in the pathogenesis (see Bearn, 1957).

INTUSSUSCEPTION IN CHILDHOOD.—There would appear to be a definite family aggregation of acute intussusception in childhood, but whether this is due to genetic factors or to the common environment is not known, MacMahon (1955) estimated the risk to sibs of an affected child to be between 15 and 20 times the incidence in the general population.

JAUNDICE (NON-HAEMOLYTIC).—There are several clinically distinct familial causes of non-haemolytic jaundice, and the number is being rapidly enlarged.

*Neonatal Hepatitis (Giant-cell Type).*—This has been studied in 38 families by Hsia, Boggs, Driscoll, and Gellis (1958), and their data are consistent with an autosomal recessive mode of inheritance. They do not, however, rule out an intrauterine factor as being responsible.

*Familial Non-haemolytic Jaundice with Kernicterus (Crigler-Najjar Type).*—This has probably an autosomal recessive mode of inheritance. Childs and

Najjar (1956) demonstrated that it is due to a metabolic block at the stage of bilirubin conjugation with glucuronic acid, the defect probably being in the enzymic system of the microsomes of the liver.

*Familial Non-haemolytic Jaundice* (*Gilbert's Disease*) is probably inherited as a dominant, the gene having incomplete penetrance. It may be that there is the same defect of bilirubin conjugation as in the disease with kernicterus, the differences in the age at onset and severity of the disease being due to their being heterozygous and homozygous for the same gene (see Arias and London, 1957).

*Dubin-Johnson Syndrome* (*Congenital Hyperbilirubinaemia with Pigment in the Liver*).—This syndrome may be inherited as an autosomal dominant, having been found in siblings and also in mother and son (Beker and Read, 1958).

PANCREATIC ISLET TUMOURS.—The role of heredity in insulin-secreting and non-insulin-secreting tumours has yet to be fully worked out. That there is a definite genetic component is suggested by the families with multiple adenomas of the pancreatic islets, parathyroids, and pituitary (Moldawer, Nardi, and Raker, 1954). It may be fortuitous that there is a high incidence of duodenal ulcer in these families with adenomatosis of endocrine glands, as there is with hereditary hyperparathyroidism (Jackson, 1959), but, in view of the well-founded association of ulcer and islet cell tumours, it seems quite possible that unrecognized hereditary endocrinopathies may be responsible for some of the familial aggregations of duodenal ulcer.

PANCREATITIS.—Hereditary chronic relapsing pancreatitis is now a well-founded clinical entity and it appears to be inherited as a dominant trait. The gene is autosomal but has not full penetrance (see Gross and Comfort, 1957). Whether or not there is a hereditary influence in the sporadic form of this disease is uncertain. Even though the onset in the familial form is younger than is usual in the sporadic, the clinical picture is similar in other respects and it may be significant that in the families most of the affected persons have been unaware of the occurrence of the disease in their relatives.

A possible association of relapsing pancreatitis with hereditary hyperparathyroidism has been reported (Jackson, 1958). Seven members of a family had hyperparathyroidism and two brothers with recurring pancreatitis were relieved of their symptoms by removal of solitary parathyroid adenomas. The familial association of parathyroid adenomas with pancreatic islet tumours (*q.v.*) is more well-founded.

There may be a relationship between familial cholelithiasis and familial pancreatitis (Rinaldo and Baltz, 1957).

PERNICIOUS ANAEMIA.—The literature contains many reports of striking concentrations of pernicious anaemia within single families, and twin studies have also suggested an inherited basis. Statistical studies have left little doubt that there is a strong inherited tendency to the disease. That this inheritance is polygenic is shown by the finding that people of group A are more likely to develop the disease than are those of group O, B, or AB (Roberts, 1957). Callender and Denborough (1957) found a remarkably high incidence of ABO non-secretors in their female patients; they did not, however, compare this incidence with that in their female controls and its significance awaits further investigation (see McIntyre, Hahn, Conley, and Glass, 1959).

POLYPOSIS OF THE INTESTINES.—A large number of families have been recorded in which intestinal polyposis is inherited as a dominant trait. In classical polyposis coli, occurring without any obvious associated lesions in other parts of the body, the responsible gene is of high penetrance (Reed and Neel, 1955). In the syndromes in which there are associated lesions, the genes are also of high penetrance though they do not always express themselves fully. The associated lesions occur without polyposis, but polyposis is not found in individuals free from other lesions. The following are probably distinct genetically as well as clinically: Polyposis coli with epidermoid cysts, fibromas, and osteomas (Gardner and Richards, 1953); polyposis coli with multiple sebaceous cysts (Oldfield, 1954); and intestinal polyposis with mucocutaneous pigmentation, the Peutz-Jeghers syndrome (Dormandy, 1957).

The possibility of a genetic basis of the common solitary polyps of the colon and rectum is uncertain, but is discussed with carcinoma of the colon.

In familial polyposis without associated superficial lesions it would be useful to have a marker gene on the same chromosome as, and close to, the gene responsible for the condition. The result of the New Zealand family study by Veale (1958) suggested that there may be such genetic linkage with the MNSs blood group genes. If this is confirmed it will be possible in some families to recognize soon after birth who has and who has not inherited the polyposis gene.

PYLORIC STENOSIS IN INFANCY.—Studies of hypertrophic pyloric stenosis in twins have shown no increased concordance in monozygotic when compared with dizygotic twins (MacMahon and McKeown, 1955). This suggests that the disease is

due to an environmental influence. On the other hand, it was found (McKeown and MacMahon, 1955) that the incidence of the disease in the offspring of people who had had it in childhood is as high as 6·9%, and in half of these offspring the affected parent was the mother. It would seem that most cases of hypertrophic pyloric stenosis are environmental in origin and occur predominantly in males, but that some cases may have a genetic basis and that these occur about equally in males and females.

STEATORRHOEA.—In the many patients diagnosed as idiopathic steatorrhoea who are suffering from adult coeliac disease, the role of heredity is presumably similar to that in childhood coeliac disease. The remainder may contain examples of genetic entities, but none has yet been discovered with the possible exception of the deficiencies of sugar-splitting enzymes. Bergqvist (1951) reported idiopathic steatorrhoea in a woman and her daughter and possibly also in her sister and son, but because of the knowledge gained since then it is now doubtful from what condition they were suffering.

STOMAL ULCER.—As most patients developing a stomal ulcer have been operated upon for duodenal ulcer, it would not be surprising to find in them a high frequency of blood group O. Doll *et al.* (1960) have, however, found that their group O frequency is even higher than that in duodenal ulcer patients. As there is probably a more direct relationship between stomal ulcer and acid than between duodenal ulcer and acid, this finding is in favour of there being a connexion between the ABO genes and gastric acidity, and that this is the reason for the increased risk of group O people of developing stomal ulcer.

SUGAR-SPLITTING ENZYME DEFICIENCY.—Amongst the causes of diarrhoea in children, three have been demonstrated as being due to deficiency of the sugar-splitting enzymes—lactase, invertase, and maltase (see Weijers, van de Kamer, Mossel, and Dicke, 1960). Though there is no information yet of any family studies, the fact that these are specific enzyme deficiencies makes it likely that they are due to single gene defects.

ULCERATIVE COLITIS.—It is as yet uncertain whether or not heredity plays a part in ulcerative colitis. Houghton and Naish (1958) review the literature and describe five families from one area with more than one case. If their estimate of the incidence in the population is correct, they think these familial aggregations are unlikely to be due to chance. It is possible, however, that the disease is commoner than they estimate and a statistical survey with good controls is needed (see also Crohn's disease).

VASCULAR MALFORMATIONS AND VASCULAR TUMOURS.—*Hereditary capillary purpura* (*Von Willebrand's disease*), in which the defect is apparently confined to the walls of the capillaries which contract inadequately on injury, is usually inherited as an autosomal dominant character (Horler and Witts, 1958).

*Hereditary Haemorrhagic Telangiectasia* (*Osler-Rendu disease*).—This is inherited as a simple autosomal dominant with good penetrance. There is some evidence suggesting that the type of lesion is also inherited; thus arteriovenous aneurysms are common in some affected families and never occur in others. Such differences may be due simply to varying expression of one gene, but are more likely to be due to different alleles, or even genes at different loci (see Annotation, 1957).

*Haemangiomas of Small Intestines.*—These have been reported by Bandler (1960) as occurring in five members of a family, and examination of the pedigree suggests an autosomal dominant mode of inheritance. The tumours were cavernous of diffuse expansive type and involved the greater part of the small intestine. In one of the individuals there was mucocutaneous pigmentation somewhat similar to that of the Peutz-Jeghers syndrome.

The angiomatosis of the small intestine, which is sometimes a part of Turner's syndrome, is presumably due partly to the missing sex chromosome which is the primary cause of the gonadal agenesia, and partly to autosomal or environmental factors modifying the expression of the genetic defect (see Annotation, 1959).

WHIPPLE'S DISEASE.—In such a rare condition as Whipple's disease the discovery of two instances of the disease in brothers makes it very likely that there are genetic factors involved. Gross, Wollaeger, Sauer, Huizenga, Dahlin, and Power (1959) have noted that out of 77 cases reported, at least six have had diabetic relatives and that mental illness also seems unusually prevalent among the relatives. They think it possible that some, if not all, patients with Whipple's disease may inherit some metabolic or other abnormality which predisposes them to this affliction.

## INDICATIONS FOR FURTHER RESEARCH

Some aspects of this subject were dealt with in the symposium organized by the Gastroenterological Research Group on "The Genetic Approach to the Study of Gastrointestinal Disease" (Annotation, 1960).

With the rare conditions which are probably due to a single gene defect, a biochemical approach is likely to be the most profitable. When the actual enzymic defect has been revealed, there is a possibility of effective prophylactic and curative therapy. Morphological abnormalities, however, are likely to be sequelae of genetically induced chemical changes during early embryonic development, and the chemical abnormality may no longer be detectable after birth.

With the more common conditions in which both heredity and the environment seem to be concerned, it may be that progress will be made by studying both genetic and environmental factors at the same time. For instance, in spite of many surveys of the various stresses to which duodenal ulcer patients have been subjected compared with controls, there is still no convincing evidence of any particular environmental factor being important. Now that the genetic basis of the susceptibility is partly understood, a further such survey might be more rewarding. Instead of simply comparing ulcer patients with normals it is now possible to make a comparison of the stresses of patients who have succumbed in spite of having the highest resistance (secretors of blood groups A, B, and AB) with those of people who have not developed an ulcer in spite of having the least resistance (group O non-secretors).

After decades of study of environmental factors, there is still a large number of diseases of uncertain aetiology, and a genetic approach is now appropriate in many of them. In particular, well-planned statistical surveys are needed in ulcerative colitis, cholelithiasis, cirrhosis of the liver, pancreatitis, steatorrhoea, appendicitis, haemorrhoids, and Crohn's disease.

A whole new field of clinical genetic research has been opened up by the discovery that the drug isoniazid is metabolized at a different rate by different people (Evans, Manley, and McKusick, 1960). The application of pharmacogenetic research to gastroenterological problems could explain why some patients respond to treatment better than do others.

The discovery that the ABO blood group genes are concerned in several disorders of the gastrointestinal tract has drawn attention to a large gap in physiological knowledge. It is quite unknown why saliva and gastric juice should have such high concentrations of the blood group antigens, but their presence cannot be fortuitous, and they must be serving some purpose. It is not even known which cells of the gastric mucosa produce the antigens, nor what are their breakdown products in the intestines. The solution of such basic physiological problems is probably necessary before the mechanism by which the blood group genes influence disease can be understood.

Perhaps the most pressing need is for more knowledge of the genetics of the physiological processes of the gastrointestinal tract. Further studies are required on the secretions of the gastric mucosa. Here at least it has been demonstrated that there is considerable variation between individuals, the range in normal people has been measured and family studies have suggested that, as would be expected, there is a genetic basis to the amount of acid which can be secreted. Sievers (1959) has made a start in trying to identify the genes concerned, and he suggests that the ABO blood group genes may be involved, not so much with the secretion of acid *per se*, as with the entire secretory activity of the gastric mucosa. Not only does this work need to be extended using normal people who have been scored for secretor status as well as blood grouped, but similar genetic investigations made of other biochemical processes, and such things as the motility of the gut.

Man is such an adaptable organism that most processes will be found to have a wide range of activity in a normal population, and the range will be genetically determined. The work of Goodman, Luke, Rosen, and Hackel (1959) is an example; studying twins they found a significant genetic influence, not only on the rate of flow, the *p*H, and amylase activity of saliva, but also on the number of microorganisms in the mouth. Some of those who are at present regarded as patients with disease entities may turn out to be individuals who have a physiological activity of a grade which is apparently pathological, but which is in reality at one end of a normal distribution curve. The first step is the study of the variation in a population, then the study of the variation within families and the identification of the gene/enzyme systems determining the variation. When such knowledge is available the basic pathology of disorders can be understood and the way will be open to really effective therapy.

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# CLINICAL AND GENETIC PROBLEMS IN FAMILIAL INTESTINAL POLYPOSIS

BY

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The history of a family suffering from familial intestinal polyposis is presented, showing how a delayed onset of symptoms together with a lack of knowledge of affected relatives may obscure the familial nature of the disease. The necessity of examining all accessible relatives, irrespective of their advancing years, is stressed. Further, it is shown that in the absence of any familial incidence the proper diagnosis of an isolated case of polyposis is that the disease is the result of a fresh mutation.

The possibility of a non-familial form of this disease cannot be proved at present and will require a special genetic investigation. It is emphasized that the diagnosis of non-familial polyposis should not be made, as this will lead to a relaxation of the vigil that should be kept on the descendants of all patients with polyposis.

The disease now known as familial intestinal polyposis was recorded in the eighteenth century, but it was Cripps (1882) who first described the condition in two siblings and suggested a familial incidence. The association of the condition with intestinal cancer had also been reported but was not generally known. The all-important fact that polyposis precedes cancer was not established until the sigmoidoscope came into general use in the first and second decades of this century. In 1925, Lockhart-Mummery published a paper which aroused widespread interest and stimulated, at St. Mark's Hospital, London, the beginnings of a research which has continued ever since. This and other investigations have shown that familial intestinal polyposis behaves as if controlled by a dominant gene although there are still many points concerning its inheritance which are still unsettled. An outstanding advance in treatment was the adoption of the operation of early colectomy and ileo-rectal anastomosis about 20 years ago, and experience has shown that this is satisfactory in many cases and especially in those where the disease is in its pre-malignant phase.

The true frequency of a familial intestinal polyposis is difficult to assess accurately. Neel (1954) placed a lower limit on its frequency in Michigan as 1 in 29,000. Later Reed and Neel (1955), using further data, amended this to 1 in 8,300 and still thought that this could be an underestimate. At St. Mark's Hospital, London, there are records of the families of 82 propositi (the index case of a family) and the disease is well known to geneticists and to surgeons specializing in intestinal diseases. Lockhard-Mummery (1925) and Lockhart-Mummery and Dukes (1939) presented data from 41 families collected at St. Mark's Hospital. It is now known that polyposis may be associated with other lesions, and pedigrees showing polyposis associated with sebaceous cysts (Oldfield, 1954), epidermoid cysts, fibromata (Gardner and Plenk, 1952) and osteomata (Gardner and Richards, 1953), and cerebral tumour (Turcot, Despres, and St. Pierre, 1959) have been described.

In addition Peutz (1921) and Jeghers, McKusick, and Katz (1949) have described a condition where polyps may be present throughout the alimentary tract but more frequently in the small intestine. This condition is associated with a spotty pigmentation of the lips, face, buccal mucosa, and the digits. It has been thought that the Peutz-Jeghers syndrome is another variant of familial intestinal polyposis, the polyps all being true adenomata and those in the large intestine showing the same tendency to undergo malignant change as in familial intestinal polyposis. Bartholomew and Dahlin (1958) and Bartholomew, Dahlin, and Waugh (1957) have cast some doubt on this theory and suggest that the polyps in the Peutz-Jeghers syndrome are the result of local tissue malformation (hamartomata) rather than true neoplasms, and accordingly there is little risk of a cancerous change.

This paper is concerned only with familial intestinal polyposis without any of these additional

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features. Dukes (1952) described fully the course of the disease and recorded details of 22 families in which there was more than one member affected. In addition there were eight families in which the details were incomplete and 11 families in which there was only one affected member. Carter (1953) suggests that these 11 cases could all be ascribed to fresh mutations, but this paper will cast some doubt on this explanation. Dukes did not suggest that any of the 11 isolated cases were fresh mutations but rather that they were non-familial phenocopies, *i.e.*, non-genetic copies of the condition, and that only long observation of the families could resolve this point. The idea of the non-familial case of polyposis is quite widely held and it has been said in support of its existence that there is no recorded instance of such a patient passing the condition on to the offspring. This is only to be expected, since the inheritance of the condition would automatically exclude the patient from that class we were seeking to establish. However, it may be that this point will be resolved in the future when a satisfactory marker for the polyposis locus is discovered. In the meantime isolated cases of polyposis will continue to arise and will always present a problem in the management of the family. Dukes (1958) has described the problems that arise in the management of a polyposis family in which several cases are known or soon discovered. This paper will present the natural history of a polyposis family and show the difficulties that may arise in making a correct diagnosis of polyposis and in establishing that there is, in fact, a familial incidence.

Gates (1946) has stated that the condition may occasionally skip a generation. This fact seems to have escaped the attention of many writers on the subject, and although Dukes (1952) recorded two instances of "skipping" he did not comment upon it. In one of these the maternal grandfather of two polyposis patients died from cancer of the colon (according to the testimony of relatives) whereas the mother died at the age of 42 from pneumonia. It may well be that the mother would have developed polyposis had she lived longer, but, as the family stands, the gene was not manifested in her. In the other case the evidence for a "skip" is not so clear but it is certainly an example of an apparently unaffected woman passing the condition to three of her children: she had two sisters who died of carcinoma of the colon. The patient herself died at the age of 44 from "ovarian tumours". Instances such as these should serve to remind us that, when the parents of a polyposis patient have died from some other cause or are alive and well and perhaps already in middle life, one must not be tempted too easily to ascribe the polyposis either to a fresh mutation or to a non-familial phenocopy.

The clinical course of the typical case of polyposis has been described many times but in all of these the natural history of the kindred has been neglected. The family to be described lives in New Zealand, and in that country all its members are now known. All living members, with only two exceptions, have been interviewed by me, some of them many times. From an acquaintance with the family extending over eight years I have been able to reconstruct the extent of the knowledge that the various members had of their relatives at different periods in the evolution of the pedigree. The first period begins with the earliest recorded death from carcinoma of the rectum and the second period covers an interval of 11 years during which further deaths occurred but the familial nature of the disease was not recognized. The third period begins with the detection of intestinal polyps and covers the first investigations of the family following the diagnosis of familial intestinal polyposis. The fourth period covers the present investigation.

The object of presenting the pedigree in this way is to show how families suffering from polyposis may easily be missed. The final pedigree as it is known today, and as it would be presented in any normal type of paper on this condition, is shown in Fig. 5, but the evolution of this family illustrates several interesting features which make the condition a difficult one to study genetically.

## Family History

First Period, 1907-1927.—It seems that the first opportunity to diagnose polyposis presented itself in 1907 when Case II.5 (see Fig. 1) died at the age of 37 from carcinoma of the rectum. This information was obtained from the records of the Registrar-General and there was no mention of polyposis. However, the subsequent history of her descendants leaves the diagnosis in little doubt. Her father had died in a shooting accident while still a young man and her mother had married again and had several children by her second husband. None of these children or any of their descendants have been affected with polyposis. Interest in the familial nature of polyposis was not widespread in 1907 but it is interesting to imagine ourselves in the position of investigating the family of this patient at the time of her death. Fig. 1 shows the family as it actually existed at this time and as the patient or one of her near relatives may have been able to report it. It is unlikely that the patient knew anything of her father's relatives in England, as her mother had emigrated with her new husband and the five children shortly after her first husband's death. An examination of II.1 and II.2 at this stage may have shown polyposis, as it is now known that these two men must have been carrying the gene. But in the light of their subsequent history it is highly probable that no polyps were present at this time.

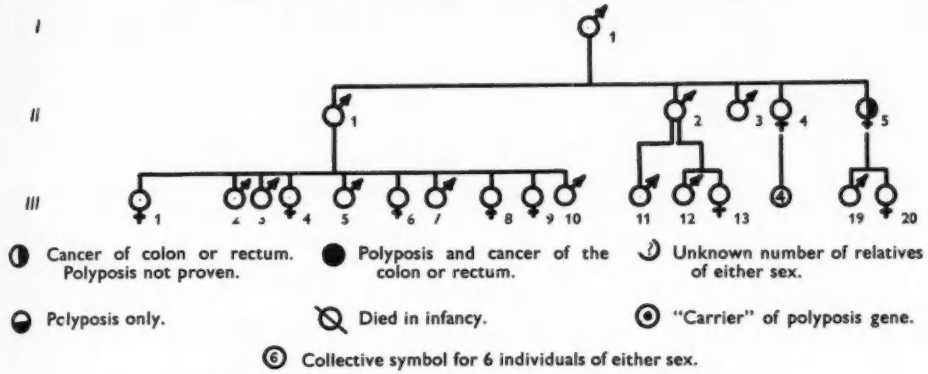
I
II
III
Cancer of colon or rectum. Polyposis not proven.
Polyposis and cancer of the colon or rectum.
Unknown number of relatives of either sex.
Polyposis only.
Died in infancy.
"Carrier" of polyposis gene.
6 Collective symbol for 6 individuals of either sex.

FIG. 1.—*The family in 1907, as it may have been known to II.5.*

SECOND PERIOD, 1928-1939.—After a period of 21 years, Case III.1 died from carcinoma of the colon at the age of 46. This was in 1928 and there is no mention of polyposis on the death certificate, but the history of some of her children again leaves little doubt that she too carried the gene for polyposis. Her father (II.1) died in 1927 from chronic bronchitis and heart failure at the age of 68 according to the death certificate. Family "lore" now has it that this man also had cancer of the bowel but this view is not universal within the family, and I think it should be disregarded in view of the information given in the death certificate, although it is clear that he also must have been carrying the gene for polyposis.

In 1934 Case III.4 died from carcinoma of the bowel at the age of 41. She had had very little in the way of symptoms and only presented in the terminal stage of her illness when the condition was found to be inoperable. If a diagnosis of polyposis had been made at this stage the information obtainable would have been meagre, as there was only one other case of carcinoma in the sibship and the patient who had died in 1907 was thought to have died from typhoid fever. In 1937, a brother (III.7) of these two women died, aged 39, from carcinoma of the rectum and the information obtainable would have been the same as before.

In the meantime there had been a further death from carcinoma in 1935 in Case III.12, then aged 34 (see Fig. 1). This man presented at hospital with a short history of bleeding per rectum with other intestinal symptoms and a loss of 28 lb. in weight over the previous five weeks. A tumour was felt per rectum and secondary deposits were palpable in the liver and elsewhere. The growth was considered inoperable and the patient died shortly afterwards. A diagnosis of polyposis was not made, but even if it had been the family history would have been of little value. From his younger unaffected brother III.14 (see Fig. 5) I have been able to ascertain that they had no knowledge of the whereabouts of any of their relatives on their father's side of the family although they knew that there were some. At the time of the present investigation (1954) Case III.14 was amazed to hear of the number of relatives that he had in other parts of the country. He was not aware that he had a half-brother. The father of this patient (II.2) had died suddenly in the street in 1929 at the age of 69 and had been examined at necropsy. The cause of death as recorded by the Registrar-General is "heart failure" and there was no mention of any pathology of the large bowel although it is clear that this man too must have been carrying the polyposis gene.

It is tragic to record that if a diagnosis of polyposis had been made during this period, and a vigorous and complete investigation of the family undertaken, several lives would undoubtedly have been saved. It should be noted here that none of the patients mentioned so far who died from cancer of the colon or rectum had an affected parent even though they came from three separate sibships. In each case the parent whom we now know to have been carrying the gene had already died from some other cause. Furthermore each of the five patients, whom we have considered presented in the terminal stages of their illness with a malignant polyp and secondary deposits already established. It is known for all these cases except the first that there were apparently no symptoms of the condition until the last few weeks of life. This absence of symptoms until the advent of malignancy has proved to be most common in this particular family.

THIRD PERIOD, 1940-1951.—It was not until 1940 that the first patient presented for medical care with a polyp. This was Case IV.41 and the family tree as known to him is shown in Fig. 2. This man was found to have a polyp 1½ cm. in diameter and 5 cm. from the anus. It was surrounded by "several" smaller polypi and the rest of the mucosa was clear up to a distance of 15 cm. The polyps were treated by diathermy excision, since when the patient has remained well but declines any further examination. From Fig. 2 it can be seen that he knew little of his relatives and nothing of their causes of death. His father (III.11) was alive and well aged 54. At this point I think it would have been a bold surgeon who would have made the diagnosis of familial intestinal polyposis as, from the patient's testimony, there was no

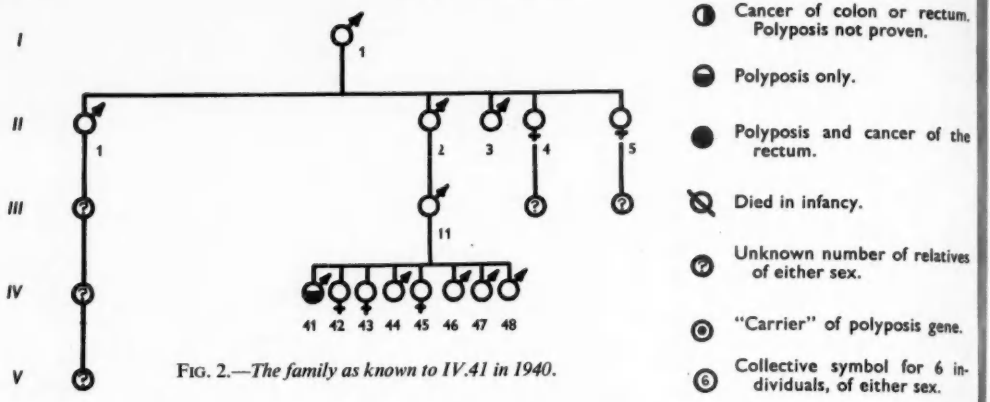


FIG. 2.—*The family as known to IV.41 in 1940.*

familial incidence at all, and, even if he had been in possession of more information, the most he could have said was that three of his father's cousins had died from carcinoma of the bowel.

This man shows clearly that it is not necessary for large numbers of polypi to be present in order to consider the possibility of polyposis. This patient had only one large polyp and "several" smaller ones but these could have provided the key to the family complaint that was still to claim further victims.

After 1940 events were to move more swiftly. In 1941, two men, Cases III.2 aged 53 and III.3 aged 49, brothers of the patients who had died in 1928, 1934, and 1937, presented with polyposis and cancer of the rectum. Both were treated by abdomino-perineal resection as a palliative measure as secondary deposits were already present. In 1942 another brother (III.5), aged 47, died of carcinoma of the colon. It was in 1941 that the diagnosis of familial intestinal polyposis was first attached to this branch of the family and an investigation of this sibship was undertaken. The pedigree as known to these patients is shown in Fig. 3. At about this time Case IV.3, living in another part of the country, had been found to have polyposis and had been treated by colectomy. Unfortunately he had died post-operatively from secondary haemorrhage.

The diagnosis of familial intestinal polyposis was now firmly established for the main branch of the family shown in Fig. 3 and a number of members were examined but with negative results. It seems now that the genetic advice given to the family at this time was misconstrued, because I found in 1952 that the majority of the family believed that they were all fated to suffer from polyposis and cancer. This led, naturally enough, to a sense of futility and a feeling of complete resignation and resistance to any investigations. When the nature of the disease was re-explained to them and the probabilities involved clarified there was a marked change in the attitude of nearly all of them. As Dukes (1958) says the information received was "good news".

In 1942 a further case of polyposis presented in the collateral branch of the family shown in Fig. 2. This was

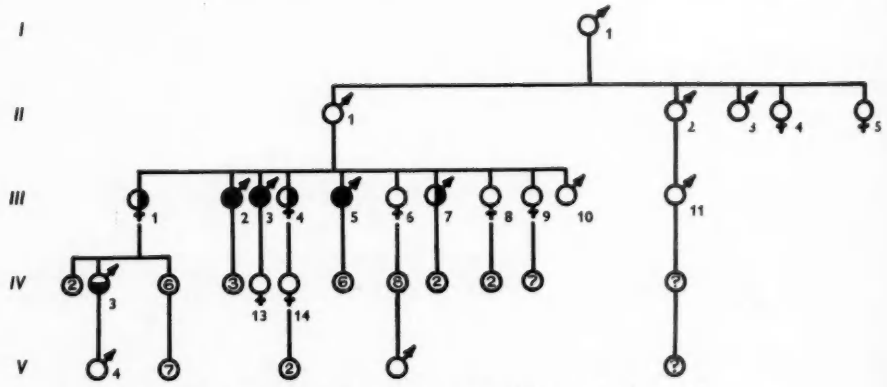


FIG. 3.—*The family as known to the sibship III.1-10 in 1942.*

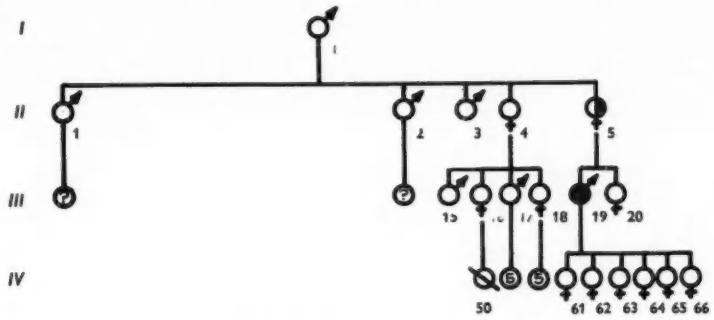


FIG. 4.—*The family as known to III.19 in 1947.*

Case IV.43 who presented to her physician, in another part of the country, complaining of bleeding per rectum. It was found that she had a prolapsed rectal polyp which was excised. This patient continued without any further symptoms until 1945 when she reported to a distant hospital with carcinoma of the rectum and secondary deposits in the liver. She died shortly afterwards at the age of 32. Her account of the family tree would have been essentially the same as that of her brother (see Fig. 2) who was seen in 1940. Her father (III.11) was now aged 59 and in robust health.

At this stage (1945) polyposis had appeared in two collateral branches of the family but the familial character of the disease had only been recognized in one (see Fig. 3). Even though each branch was aware of the existence of the other the contact between them was minimal and certainly did not extend to a knowledge of intimate medical detail. Because of this no investigations were made of the branch shown in Fig. 2.

In 1947, a new case of polyposis arose in a hitherto unaffected branch of the family in another part of the country. However, the diagnosis of familial intestinal polyposis was made and a family investigation undertaken but no new cases of polyposis were found because of the patient's ignorance of the existence of his affected relatives. The affected man was Case III.19 and his account of the family is shown in Fig. 4. The patient died of carcinoma of the colon in 1947 at the age of 43 and local medical interest in the family waned until 1954.

FOURTH PERIOD, SINCE 1952.—Other cases continued to arise in the branch of the family shown in Fig. 3, and it was as a result of one of these that my own interest was aroused and a complete investigation of the family undertaken. The ultimate linking up of the branch of the family shown in Fig. 3 with that shown in Fig. 4 was only possible after information was received from a descendant of the wife of I.1, following her second

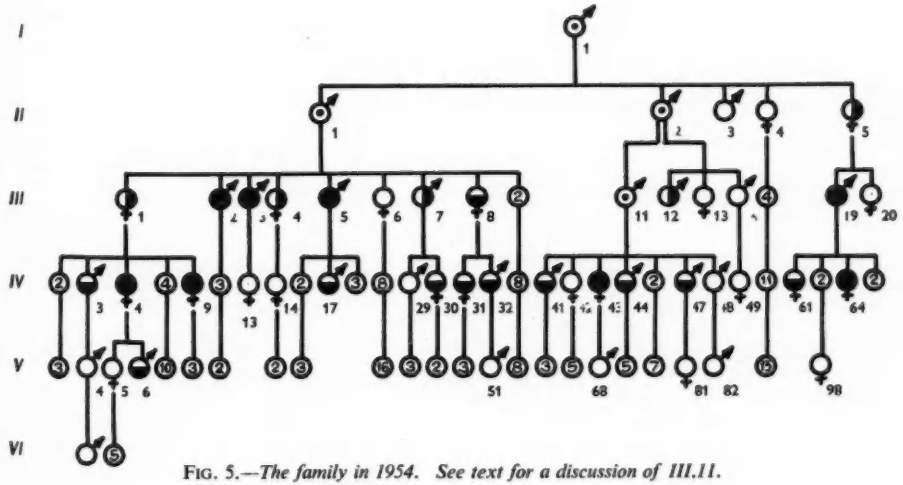


FIG. 5.—*The family in 1954. See text for a discussion of III.11.*

marriage. As a result of this investigation the complete pedigree was established and all members over the age of 16 were asked to submit to sigmoidoscopy and *x*-ray examinations. Patients younger than this were examined at the request of parents. Several new cases of polyposis were discovered and in one of these (IV.64), a girl of 18, a carcinoma was already present.

The family as it existed in 1954, is shown in Fig. 5 and interest naturally enough focused on III.11 who was still alive and well aged 68. I saw this man first in 1952 and found a vigorous, slightly overweight farmer still leading an active working life. Unfortunately I was never able to persuade him to submit to any kind of examination. He remained friendly and cooperative on all other matters, saying that he had never had anything to do with hospitals during his life and he wasn't planning to begin now. He always maintained, until I saw him for the last time in 1954, that he was perfectly well and had no symptoms at all. During 1956 he began to lose weight and later became jaundiced. He eventually died early in 1957 at the age of 71. The efforts of one of his daughters, who appreciated the genetic interest of her father's condition, overcame some family opposition and a necropsy was performed. The peritoneal cavity, stomach, and small intestine were all normal. In the large bowel, small polyps, generally less than 5 mm. in diameter, were scattered sparsely throughout its length. In the transverse colon there was a larger pedunculated tumour 3 cm. in diameter. In the rectum there was a massive ulcerating tumour involving subserous tissues, lymph nodes, and veins. The liver was enormously enlarged by multiple deposits of tumour tissue.

This patient provides clear evidence of the necessity of examining everyone who may be carrying the polyposis gene. No person should be omitted because they are symptomless or have reached an age beyond which the probability of polyposis is commonly and erroneously believed to be unlikely. The fact that symptoms may be delayed until the age of 70 is not readily apparent from the literature as it is usually those families showing a striking incidence in the younger age groups which are reported. Such a delay in the onset of symptoms increases the chances of these persons dying from other causes, so that the subsequent appearance of polyposis in one of their progeny may be regarded erroneously as the result of a fresh mutation. Since we have seen how misleading a family history can be, this interpretation of the isolated case should not be made without a full investigation and examination of all accessible relatives. If no evidence is obtained of a family incidence, then it is proper to conclude that an isolated case of polyposis may be the result of a fresh mutation and the full genetic situation should be explained to the patient so that in time any offspring can be examined in their turn. It should never be concluded that a case is a non-familial phenocopy, as this will automatically lead to a relaxation of the vigil that should be kept on descendants, possibly with tragic results. That fresh mutations do occur is not doubted but the frequency with which this is likely to happen will not be discussed here. The estimation of the mutation rate depends on the incidence of the condition in the general population and on the relative biological fitness of the individuals affected.

There is a further question which arises from a study of this family and that concerns the factors conspiring to bring about the considerable delay in the onset of symptoms in some patients but not in others. There have been no striking differences in environment within the family over the last 40 years so it may be that the observed differences in behaviour of the polyposis gene are due to differences in the total genetic background on which it plays. Whether this difference affects the number of polyps, their time of appearance, or their tendency to undergo malignant change cannot all be answered from one pedigree but more extensive material may throw some light on these questions.

I wish to express my gratitude to the New Zealand Medical Research Council for a research grant.

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# THE DISTRIBUTION OF ULCERATIVE COLITIS AND REGIONAL ENTERITIS IN UNITED STATES VETERANS WITH PARTICULAR REFERENCE TO THE JEWISH RELIGION

BY

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In a sample of patients, discharged from Veterans Administration Hospitals in the United States, suffering from ulcerative colitis and regional enteritis and mixed forms of these diseases, the proportion of Jews was four times as high as in a corresponding sample of general medical and surgical patients.

In the course of a study of the distribution of ulcerative colitis and regional enteritis in U.S. veterans an apparent excess of patients professing the Jewish religion was noted. In view of the differences of opinion expressed in the literature as to whether or not these diseases are unduly prevalent in Jews this point was examined in detail.

## Material

Data were obtained for all 2,320 male veterans discharged from the 174 hospitals of the Veterans Administration with a diagnosis of regional enteritis (572·0) or chronic colitis or enteritis not specified as ulcerative (572·3) from 1953 to 1957, and for ulcerative colitis (572·2) for 1956 and 1957 (World Health Organization, 1948-49). The patients were then classified according to the words used in the discharge diagnosis into five groups as seen in Table I. A detailed study of the clinical records of 81 of these patients in a related investigation (Acheson, 1960a) had demonstrated a high standard of investigation and diagnosis in the ulcerative colitis and regional enteritis groups. No further records were examined in this study.

## Method

The distribution of the 2,320 patients in terms of religion, race, and birth place was compared with that of a 12·5% sample of all patients discharged in October, 1956, with general medical and surgical conditions. This sample consisted of 4,072 veterans. A 25% sample of all such discharges (7,705 patients) in February, 1956, was also used to confirm the overall proportion of Jews.

## Results

Table I shows that approximately four times as many Jews were found among veterans with regional enteritis and ulcerative colitis as among the sample of all discharges for general medical and surgical conditions. A similar excess of Jews was found in the group of patients suffering from enterocolitis and various combinations (mixed forms) of the two diseases. On the other hand, in the ill-defined conditions described as "chronic enteritis" and "chronic colitis" the proportion of Jews was similar to that in the control group.

The table also shows that the proportion of negroes discharged with any of the diagnoses under study except chronic enteritis was materially smaller than the proportion in the sample of all discharges. However, even when this is taken into account and the number of Jews in each diagnostic group is expressed as a proportion of all whites, the striking excess of Jews with ulcerative colitis, regional enteritis, or mixed forms remains. This excess could also be demonstrated when World War I veterans, and veterans of World War II and the Korean conflict were compared separately with the corresponding groups in the control sample. This analysis was necessary because the control group as a whole was older than the test group. It permitted comparable age groups to be studied.

As the Jewish population of the United States is concentrated in the north-eastern part of the country, it was important to determine whether the apparent excess of Jews suffering from the diseases under study was due to a localization of these diseases in the north east. A suggestion of such a

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TABLE I

COMPARISON OF NOS. OF JEWISH PATIENTS DISCHARGED FROM VETERANS HOSPITALS WITH VARIOUS DIAGNOSES AND NOS. IN A SAMPLE OF ALL GENERAL MEDICAL AND SURGICAL DISCHARGES

| | Professing Hebrew Religion | | | Number of White | Negroes | | Total No. of Cases (All Races) |
|---|---|---|---|---|---|---|---|
| | No. | % of White | % of All Cases | | No. | % | |
| Regional enteritis | 65 | 9·3 | 8·8 | 698 | 44 | 5·9 | 742 |
| Chronic enteritis not specified as regional | 1 | 1·5 | 1·2 | 65 | 16 | 19·8 | 81 |
| Ulcerative colitis | 111 | 9·8 | 9·4 | 1,129 | 46 | 3·9 | 1,175 |
| Chronic colitis not specified as ulcerative | 3 | 1·5 | 1·4 | 195 | 16 | 7·6 | 211 |
| Mixed forms* | 9 | 8·6 | 8·1 | 105 | 6 | 5·4 | 111 |
| Sample of general medical and surgical discharges, October, 1956 | 80 | 2·3 | 2·0 | 3,469 | 603 | 14·9 | 4,072 |

* Ulcerative colitis and regional enteritis together; chronic enterocolitis, ulcerative colitis specified as involving the ileum; regional enteritis specified as involving the colon.

TABLE II

PROPORTIONS OF JEWS AMONG WHITES WITH ULCERATIVE COLITIS AND REGIONAL ENTERITIS BY GEOGRAPHICAL REGION OF BIRTH COMPARED WITH PROPORTIONS IN SAMPLE OF ALL GENERAL MEDICAL AND SURGICAL DISCHARGES

| Geographical Region of Birth* | Ulcerative Colitis | | | Regional Enteritis | | | Sample of All General Medical and Surgical Discharges | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of Jews | % Jews | Total Whites | No. of Jews | % Jews | Total Whites | No. of Jews | % Jews | Total Whites |
| North east | 71 | 20·1 | 353 | 43 | 20·0 | 215 | 51 | 6·6 | 772 |
| North central | 20 | 5·3 | 376 | 11 | 5·9 | 188 | 3 | 0·3 | 1,006 |
| South | 3 | 1·2 | 252 | 2 | 1·0 | 203 | 3 | 0·2 | 1,209 |
| West | 3 | 3·2 | 95 | 0 | 0·0 | 55 | 1 | 0·5 | 190 |
| Foreign born | 14 | 26·4 | 53 | 9 | 33·3 | 27 | 22 | 7·5 | 292 |
| Totals | 111 | 9·8 | 1,129 | 65 | 9·3 | 698 | 80 | 2·3 | 3,469 |

* As defined by the Bureau of the Census, U.S. Department of Commerce.

distribution had been found by Acheson (1960b, 1960c) in studies of the deaths attributed to these diseases in the United States. Table II gives the proportions of Jews with ulcerative colitis and regional enteritis in the four geographical regions of the country compared with the control group. The cases have been distributed by region of birth. A higher proportion of veterans with ulcerative colitis and regional enteritis are Jewish than in the control group regardless of the region of birth within the United States: this generalization extends to foreign born veterans. The single exception (patients with regional enteritis born in the west) may be due to the small numbers involved.

## Discussion of Results

The differences in the proportions of Jews with ulcerative colitis, regional enteritis, or mixed forms of these diseases as compared with a sample of all discharges of general medical and surgical cases might be explained by (1) a bias in the sample of such discharges resulting in a decrease in the proportion of Jews contained in it; (2) a tendency for Jews with ulcerative colitis or regional enteritis to seek hospital treatment in veterans' hospitals to a greater extent than those suffering from other general medical and surgical conditions; (3) a real excess of Jewish sufferers from these conditions, or a form of the disease requiring more frequent admission to hospital in these people. In case the October general medical and surgical discharges were not representative of the period under study, a count was also taken of all Jewish patients discharged in February, 1956. The proportion of 2·2% (167 of 7,705 patients) found was almost identical to that in the October sample and disposes of the first objection. The second argument, while difficult to refute, seems highly unlikely. It therefore seems probable that the results reported here indicate either that these diseases are more prevalent or are more severe among Jews than among other whites. A certain amount of support can be obtained for the former view from the literature. Sloan, Bargen, and Gage (1950) found that 9·4% of 2,000 ulcerative colitis patients treated at the Mayo Clinic were Jewish. Paulley (1950) compared the proportion of Jewish patients with ulcerative colitis in two London hospitals with the proportion of Jews found among all patients discharged. He found twice as many Jews among the ulcerative colitis patients.

In the original description of regional enteritis by Crohn, Ginzburg, and Oppenheimer (1932), all 14 patients were Jewish. However, when reflecting

on the developments which had occurred over the next 20 years, Crohn and Janowitz (1954) felt that "no ethnic group preponderates". Boyce (1955), in his monograph, disagrees and states that the disease is more prevalent in Jews. Van Patter, Bargen, Dockerty, Feldman, Mayo, and Waugh (1954) reporting 600 cases from the Mayo Clinic found 153 Jews (25·5%). The figure mentioned by Ruble, Meyers, and Ashley (1957) is even higher; they found that 43 of 100 patients at the Harper Hospital were Jews. In view of the fact that neither of these institutions are Jewish foundations these figures are remarkable even in the absence of information about the ethnic structure of the overall hospital populations.

It is not known whether the apparently increased susceptibility of Jewish persons to ulcerative colitis and regional enteritis demonstrated here is due to an hereditary or an environmental influence. It would be interesting to know the relative prevalence of the diseases in Ashkenazic and Shephardic-Oriental Jews, and among those who do and do not adhere strictly to the dietary law (Kallner, 1958; Dorn, 1959).

## Conclusions

The proportion of Jews in samples of patients discharged from Veterans Administration hospitals with ulcerative colitis, regional enteritis, and mixed forms of these diseases was about four times higher than in samples of all general medical and surgical patients.

No excess was found in the proportions of Jews with chronic colitis not specified as ulcerative, or with chronic enteritis not specified as regional.

When the cases of ulcerative colitis and regional enteritis were distributed by geographical region of birth a higher proportion of Jews with ulcerative colitis or regional enteritis than in the control group was noted in every region except one.

Dr. M. T. Musser and Dr. C. A. Bachrach offered valuable criticisms. I wish to thank Mrs. H. Bickley for her help in preparing the tables and manuscript.

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# AN ASSESSMENT OF THE VALUE OF SERUM CHOLINESTERASE AS A LIVER FUNCTION TEST AND IN THE DIAGNOSIS OF JAUNDICE

BY

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This report assesses the value of cholinesterase (ChE) activity as an indicator of liver function and analyses its usefulness in the diagnosis of jaundice. A rapid method of determination has been used, and alterations in ChE activity in conditions other than liver disease have been studied to permit a fuller and more accurate survey of its value as a liver function test.

The level of serum cholinesterase activity remains constant under normal circumstances, and follows the pattern of protein metabolism, falling in catabolism and rising in anabolism.

In hepatocellular disease cholinesterase activity is lowered. Very low levels in cirrhosis with jaundice indicate a grave prognosis. Normal levels are usual in post-hepatic jaundice unless complicating factors are present, such as cholangitis or liver metastases.

Serum cholinesterase is useful both as a liver function test and in the diagnosis of jaundice provided consideration is given to the other factors which affect the level of activity of the enzyme.

Estimation of the level of activity of the cholinesterase (ChE) found in serum was first suggested by McArdle (1940) as a useful means of differentiating hepatic from post-hepatic jaundice. He found low enzyme activity in jaundice of hepatic origin, and his observations have since been confirmed by others (Alcalde, 1950; Vorhaus, Scudamore, and Kark, 1950; Mann, Mandel, Eichman, Knowlton, and Sborov, 1952; Wilson, Calvert, and Geoghegan, 1952; Kaufman, 1954). Most workers have reported unimpaired ChE activity in post-hepatic jaundice.

The expectation that ChE activity would prove a useful test in the differential diagnosis of jaundice was not realized, mainly because of the difficult techniques involved in the early biological and chemical methods of assay. Final agreement has thus not yet been reached on the diagnostic value of ChE.

## Method

A slight modification of the electrometric method described by Michel (1949) has been used in this study. In this method, which is simple and accurate, ChE activity is measured indirectly. The principle of the method is that ChE in serum hydrolyses a buffered solution of acetylcholine bromide, and the level of ChE is estimated indirectly by the amount of acetic acid produced. This is measured by the change in *p*H which occurs in an assay tube over a definite period of time during which a known volume of serum is incubated with an excess of substrate. The results are expressed in delta *p*H units per hour. The reagents used were as described by Michel (1949).

## Procedure

Serum is obtained by centrifuging a specimen of clotted blood collected in a chemically-clean test tube. If the red blood corpuscles and serum are not separated, haemolysis occurs, and falsely high levels of ChE are obtained, as the ChE of corpuscles is present at a higher concentration than the ChE of serum (Callaway, Davies, and Rutland, 1951). The serum is frozen and preserved at $-15$°C. for a period of up to five days, if the estimation cannot be carried out immediately. The enzyme does not alter its activity during this time. (Molander, Friedman, and La Due (1954) showed that frozen sera gave reproducible results at monthly intervals over a period of several months.)

Freshly prepared working buffer at *p*H 8·00, 40 ml., is added to a test tube in a water-bath at 25°C., and allowed to equilibrate for 10 minutes. After pre-incubation at 25°C. for the same time 4 ml. of acetyl choline bromide is added. Finally, 0·4 ml. of serum is added, the solution mixed in the tube, which is now stoppered, and the time noted. Incubation is carried out for one hour at 25°C. $\pm$1°C. It is quite essential for the temperature in the water-bath to remain constant at 25°C. $\pm$1°C. during the incubation period, otherwise the reaction velocity alters sufficiently to invalidate any results. The reaction is then stopped by placing the tube in an ice-bath. The final *p*H of the assay solution is read

and compared with the *p*H of a control which does not contain serum. The difference represents the drop in *p*H due to the production of acetic acid by enzymatic hydrolysis. The use of a control for each set of estimations allows for the calculation of the small but definite amount of non-enzymatic hydrolysis which usually occurs.

Michel has given a table of factors to correct for the effect of a varying *p*H on the specific activity of ChE. When detailed investigations of small differences in ChE activity are being studied, this factor is employed. However, as it is insignificant, it is not used when ChE is being used as a test of liver function as only gross alteration from the normal is important in these circumstances.

### Reliability of the Method

In a consecutive series of 231 ChE estimations carried out in duplicate, both assay tubes gave identical readings in 32·4%, a difference of 0·02 *p*H unit in 52·8%, and a difference of 0·04 *p*H unit in 14·6%.

### Results

**Serum Cholinesterase Activity in Healthy Adults.**—ChE activity was measured in 50 healthy adult blood donors. The distribution of values is shown in Fig. 1. The observed range lay between 0·46 and 1·37 delta *p*H units per hour, with a mean value of 0·95 and standard deviation of $\pm$0·20. The normal range was considered to be 0·95 $\pm$ 0·40 (0·55 $\rightarrow$ 1·35) delta *p*H units/hr. These values are very similar to those reported by Vorhaus *et al.* (1950), who reported a mean of 0·94, a standard deviation of 0·16, and a normal range of 0·68 to 1·37. Other workers have reported mean normal values for serum or plasma ranging from 0·703 (Michel, 1949) to 1·11 (Aldridge and Davies, 1952).

An implication of the wide range of normality is that care is required in interpreting a single reading in a patient unless it is clearly beyond the normal range. A value may be within the normal range and yet be abnormal for the patient being studied.

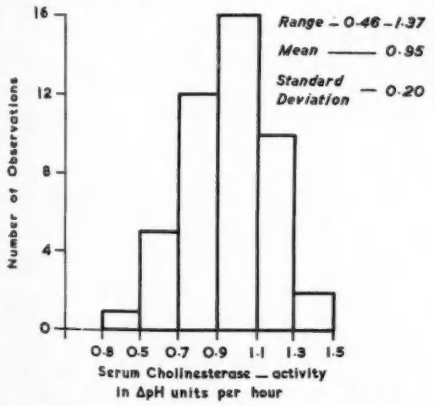


FIG. 1.—*Range of serum cholinesterase activity in 50 healthy adult blood donors.*

**Constancy of Serum Cholinesterase in the Individual.**—The level of activity of ChE in eight hospital patients over a period of 15 days was studied, in order to determine the constancy or otherwise of the level in the individual subject. None of these patients had liver disease, or was being subjected to any drug therapy or operation which might have affected the results.

The results show a remarkable constancy in each individual over the period of 15 days (Table I). On only one day, the third, was there any significant difference between initial and subsequent values. This difference was common to all patients and was due to an instability of the *p*H meter on that day. It seems, therefore, that each individual has his own particular level of ChE which remains fairly constant. In one patient (No. 4) the level was held at a value near the lowest range of normality.

TABLE I

CHOLINESTERASE ACTIVITY (DELTA *p*H UNITS/HR.) OVER 15 DAYS IN PATIENTS WITH NO LIVER DISEASE

| Patient | Day of Observation | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 3 | 6 | 8 | 10 | 13 | 15 |
| 1 | 0·82 | 0·94 | 0·80 | 0·84 | 0·90 | — | — |
| 2 | 0·99 | 1·14 | 0·89 | 0·96 | 1·00 | 1·10 | 1·06 |
| 3 | 0·94 | 1·03 | 0·87 | 0·89 | 0·84 | 0·98 | 0·93 |
| 4 | 0·64 | 0·80 | 0·61 | 0·72 | 0·62 | 0·63 | 0·60 |
| 5 | 0·87 | 1·08 | 0·92 | 0·91 | 0·92 | 0·97 | 0·91 |
| 6 | 0·57 | 0·69 | 0,61 | 0·68 | 0·62 | 0·59 | 0·65 |
| 7 | 1·04 | 1·13 | 0·99 | 0·99 | 0·94 | 0·93 | 0·91 |
| 8 | 0·89 | 0·99 | 0·90 | 0·96 | 0·84 | 0·97 | 0·92 |

### Alteration in Serum Cholinesterase Activity by Factors other than Hepato-Biliary Disease

**Effect of Anaesthesia and Operation.**—A study was made of alterations in ChE activity which occurred after operation. Similar observations on a number of other liver function tests were carried out at the same time for comparison. Thirty-four of the operations were considered major and 16 minor. No attempt was made to influence the choice of anaesthesia in current use. Blood samples were obtained for analysis for ChE before and after operation, on the morning of the first post-operative day, and every second morning thereafter for 14 days.

The mean ChE values for all 50 cases on the various days of estimation are shown in Fig. 2. There was an insignificant drop from 0·94 to 0·90 during the operation. A fall occurred in the days immediately after operation, the lowest value being

reached on the fifth post-operative day. This fall was statistically significant ($P<0.1$). By the thirteenth day this value had not increased, and so was still significantly below the original mean value. This drop in ChE activity occurred after both major and minor operations. In all, 31 cases out of 50 showed a fall of ChE greater than 30% of the initial value. There was no correlation between the percentage fall in ChE and the type or duration of the operation, the anaesthetic agents used, or the blood loss. An increased output of urinary urobilinogen was observed at the time of the fall in ChE and low values of ChE were associated with the development of a positive cephalin cholesterol flocculation.

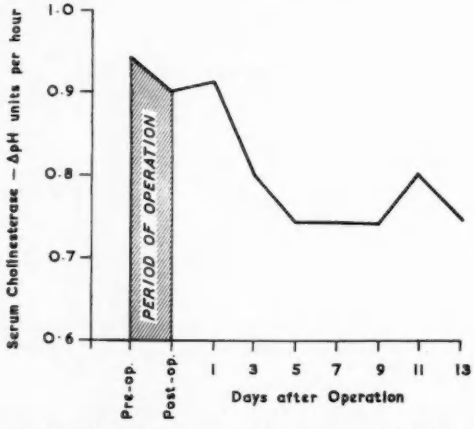


FIG. 2.—*Changes in serum cholinesterase activity during and after operation (mean values for 50 patients).*

EFFECT OF TRAUMA.—Serial observations of ChE activity were carried out in patients who had sustained a fracture of the femur. Estimations were made on admission and weekly thereafter for eight to 10 weeks in seven patients. In six out of seven, a fall occurred in the first week, followed by a gradual rise over the ensuing weeks until the level had reached or even surpassed the original figure. In each patient, the level on admission to hospital, a few hours after the fracture was sustained, was considered the normal value for that individual patient.

The course followed by three patients is shown in Fig. 3. Case I shows the normal pattern which was observed. A fall is evident one week after injury, followed by a steady rise to normal level as the fracture healed with no complications. In Case II, the initial fall was followed by two further falls which were directly related in time to the occurrence of pneumonia, and subsequently to the development of a severe cystitis and ascending urinary infection which led to the patient's death. Case III shows two falls, the first in the period immediately after fracture, the second during the first week after pinning of the fractured neck of femur. This second fall corresponds to the post-operative changes described above.

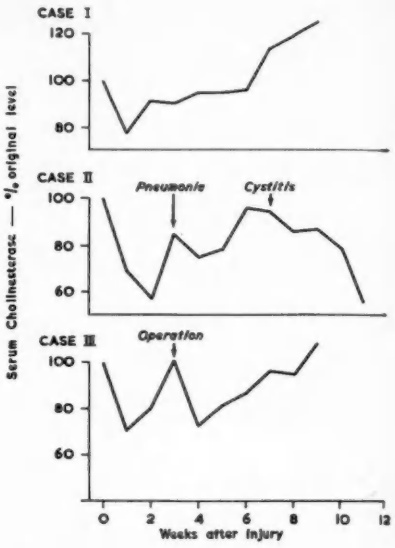


FIG. 3.—*Serum cholinesterase activity in three patients after fracture of the femur.*

EFFECT OF *X*-RAY THERAPY.—The effect on the level of circulating ChE was studied in a series of 12 patients who were being treated by *x*-ray therapy after mastectomy. The results are summarized in Table II, which also gives the dosage of deep therapy

TABLE II

SERUM CHOLINESTERASE LEVELS DURING COURSE OF *X*-RAY THERAPY AFTER MASTECTOMY FOR CARCINOMA OF BREAST

| Case No. | Breast Treated (L or R) | Maximum ChE Fall (%) | Day of Maximum Fall | Symptoms of Radiation Sickness |
|---|---|---|---|---|
| 1 | L | 31 | 16 | 0 |
| 2 | L | 22 | 9 | +++ |
| 3 | R | 15 | 11 | ++ |
| 4 | R | 0 | — | 0 |
| 5 | R | 27 | 12 | +++ |
| 6 | L | 37 | 16 | + |
| 7 | L | 32 | 16 | +++ |
| 8 | R | 45 | 17 | +++ |
| 9 | L | 30 | 9 | ++ |
| 10 | L | 0 | — | + |
| 11 | R | 0 | — | + |
| 12 | R | 10 | 15 | + |

Dosage: 3,750 r. central axis dosage to axilla.
3,750——→4,274 r. glancing fields to chest.

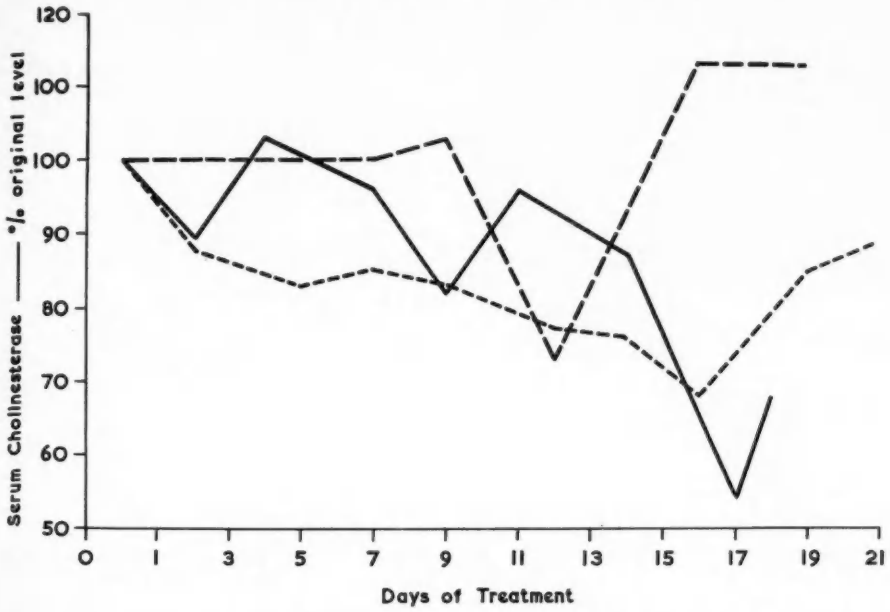


FIG. 4.—*Alterations in serum cholinesterase activity in three patients undergoing x-ray therapy after mastectomy for carcinoma of the breast.*

used. However, the observed effects on ChE presumably reflect the "integral rate" which will have varied with the physical size of each patient. A fall in ChE was found in nine of the 12 patients. Typical examples of this are shown in Fig. 4. Very little change occurred during the first week, but ChE fell obviously during the second and third week. In each individual, there was a striking correlation in time between a fall in ChE and the occurrence of nausea and vomiting.

THE ACUTE ABDOMEN.—ChE was estimated in a series of cases admitted with acute abdominal pain to a surgical ward. Blood was obtained from a vein shortly after the patient's admission and before the administration of any drug. After separation of the serum, it was kept at −15°C. until the estimation was carried out at a convenient time during the next 24 hours. In acute appendicitis, 50 observations were made and most of these lie within the normal range. Only four were found just below the lower limit of normal. It is of interest that three of those four patients had experienced symptoms over a period of some days and had developed an appendicular abscess. A further three patients with appendicular abscess had ChE levels of activity near the lower limit of normal. Thirteen cases of perforated duodenal ulcer were studied and showed a scattered distribution within the normal range. There was no correlation between the degree of peritoneal contamination and the level of ChE activity. In 18 cases of intestinal obstruction, there was again a scattered distribution of levels of activity. Particularly low values were found in two cases. A level of 0·32 was found in a patient with intestinal obstruction and strangulation, and one of 0·38 in a patient who had very extensive mesenteric thrombosis with gangrenous change in a large portion of the intestine. A scattergram of the above results is shown in Fig. 5, which also includes a comparison with ChE levels in 10 patients with chronic infection in whom the ChE level tended to be low. The six points on the scattergram representing the patients with appendicular abscess have been ringed for comparison with the other cases of appendicitis of short duration and the 10 cases of chronic sepsis.

ACUTE PANCREATITIS.—Observations were made in 11 cases of acute pancreatitis. The value of ChE on admission was normal in every case. However, it fell dramatically in three patients

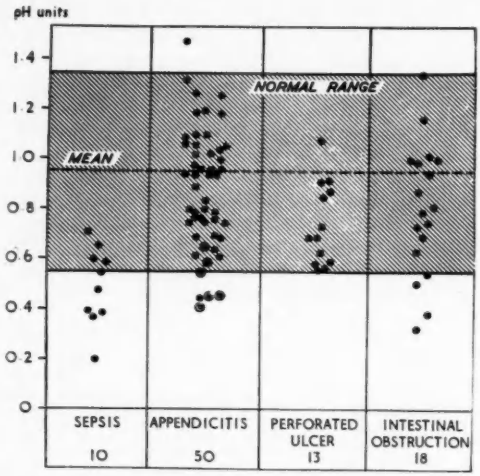


FIG. 5.—*Serum cholinesterase activity in chronic sepsis and acute abdominal disease. Each point represents one patient, and the six ringed points indicate patients with appendicular abscess.*

in whom serious clinical deterioration occurred.

A man, aged 46, presented with severe abdominal pain of 12 hours' duration. The abdominal wall was as rigid as a board, and a diagnosis of perforated peptic ulcer was made. At operation a haemorrhagic pancreatitis was found. Serum amylase on admission was 3,200 Somogyi units. The ChE level on the day of admission was 0·83. By the following day it had fallen by more than 50% to 0·40.

This patient, a woman aged 51, had a 12 hours' history of severe abdominal pain of sudden onset, radiating through to the back and associated with much nausea and vomiting. A diagnosis of acute pancreatitis was made, the serum amylase on admission being 3,200 Somogyi units. No operation was carried out. The ChE level on admission was 0·90 but had fallen by the next day to the very low level of 0·15. This patient subsequently died. Post-mortem examination showed that a haemorrhagic pancreatitis had completely destroyed the pancreas.

A woman, aged 59, was admitted following a six hours' history of severe abdominal pain of sudden onset accompanied by much nausea. Serum amylase on admission was 2,560 Somogyi units, and laparotomy confirmed the presence of haemorrhagic pancreatitis. The ChE level on admission was 0·90. This fell gradually in the course of the next three days to 0·65 and finally on the 24th day of a severe illness, complicated by a pancreatic fistula and pleural effusion, the value had dropped to 0·16.

EFFECT OF PROLONGED INFECTION.—The effect of prolonged infection on ChE activity was studied in 10 cases. These included such conditions as perinephric abscess, peridiverticular abscess, cellulitis of the leg, and pancreatic abscess. All infections had been present for at least one week and usually much longer, and all were causing marked constitutional upset. The levels of ChE in this group are shown in Fig. 5 where they are compared with the results in acute abdominal conditions. In six of the patients with chronic sepsis, the ChE level was found to be below the lower limit of the normal range; in the remaining four it was in the lower range of normal. When comparison is made with appendicitis (FIG. 5) it is noticeable that cases of inflammation of short duration (the majority of this group) lie in the normal range. On the other hand, low values were consistently seen in appendicular abscess where infection had been present for a longer period of time corresponding to the period of infection in the group of patients with chronic sepsis.

## CHOLINESTERASE ACTIVITY IN HEPATO-BILIARY DISEASE

CHRONIC CHOLECYSTITIS.—Estimations were made on 26 patients on their admission to hospital for elective cholecystectomy. None were jaundiced. Levels of ChE activity ranged from 0·97 to 1·83 delta *p*H units/hr. The mean value was 1·35 (the highest value in the normal range). Ten patients out of 26 had a value above the limit of normal, and none were significantly below the normal mean. In no other conditions were high values regularly observed.

ACUTE CHOLECYSTITIS.—In acute cholecystitis, estimations were made on seven patients who were not jaundiced. The range of activity lay between 0·83 and 1·27. The mean was 1·02. In view of the fact that inflammation has been shown to be accompanied by lowered ChE activity, it is worthy of note that these values are lower than those given above for chronic cholecystitis, but the mean is still somewhat above the normal mean of 0·95.

NON-MALIGNANT DISEASE OF LIVER.—In cirrhosis, ChE was found to be low, the range being from 0·06 up to the lower limit of normal with a mean of 0·31 in seven cases. A level of 0·97 was found in a patient with presumed cardiac cirrhosis. Normal levels were found in two patients with reticulosis and one who was suffering from chronic alcoholism.

METASTATIC CARCINOMA OF LIVER.—Twenty-four patients with metastatic deposits in the liver have been studied. The range of activity lay between 0·20 and 1·20 delta *p*H units/hr. The mean was 0·52, a level below the lower limit of the observed normal range (0·55). Seventeen patients (70·8%) had levels of activity at or below this figure; only one was above the normal mean level of 0·95.

TABLE III
SERUM CHOLINESTERASE IN HEPATIC JAUNDICE

| Diagnosis | No. of Cases | Range (Delta *p*H units/hr.) | Mean |
|---|---|---|---|
| Cirrhosis | 14 | 0·03 to 0·57 | 0·28 |
| Hepatitis | 7 | 0·00 to 0·72 | 0·44 |
| Others | 13 | 0·15 to 1·26 | 0·75 |
| Total | 34 | — | 0·49 |

HEPATIC JAUNDICE.—Studies were made on 34 patients with varying types of hepatocellular disease. The results are summarized in Table III. In 24, the ChE level was below the lower limit of normal: in three others it was approximately at this level, a total of 79·4% of those examined. In viral hepatitis, ChE activity ranged from 0· to 0·53 in six out of seven patients. In this group, a considerable systemic upset was present. The seventh patient had a relatively mild hepatitis, and had a recorded ChE of 0·72 well within the normal range. In cirrhosis with jaundice, 13 out of 14 patients had ChE levels of less than normal activity; in some, only slight evidence of ChE activity was found. The results obtained in hepatitis and cirrhosis are given in Fig. 6 where they are compared with those obtained in patients with stone in the common bile duct and biliary tract carcinoma.

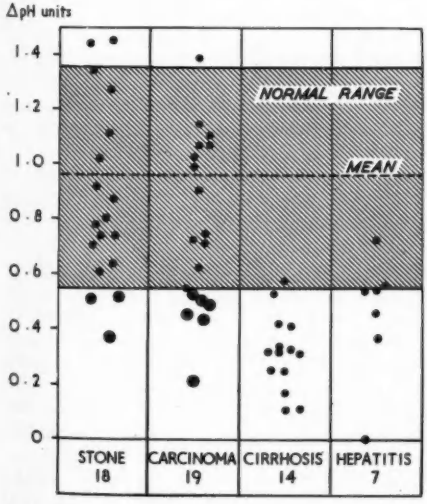


FIG. 6.—*Serum cholinesterase activity in jaundice, comparing the levels in the principal causes of hepatic and post-hepatic jaundice. Each point represents one patient, and the ringed points a complication of post-hepatic jaundice, namely, cholangitis, biliary cirrhosis, or metastases in the liver.*

In general ChE activity mirrored the severity of the clinical condition. This is illustrated by the following two case histories. In the first patient, ChE activity was 0·15, an extremely low level. This patient, who had no previous history of illness, died shortly afterwards in hepatic coma from liver cell failure. The second patient, whose ChE was 1·21, high in the normal range, was a young man, aged 25, who was never acutely ill but had recurrent bouts of jaundice and tiredness. He was in all probability suffering from the cholangiolitic form of hepatitis.

In toxic hepatitis, the following results were obtained in three patients:—

| | | ChE |
|---|---|---|
| 1 | Chlorpromazine jaundice | 1·14 |
| 2 | Chronic mild carbon tetrachloride poisoning | 1·26 |
| 3 | Nitrogen mustard therapy for metastatic carcinoma | 0·57 |

The first two patients had only minor symptoms apart from jaundice and at no time did their condition give any cause for anxiety. The third patient developed jaundice following intravenous nitrogen mustard therapy for advanced carcinoma with hepatic metastases, so that the relatively low value might have resulted from the presence of these metastases.

Three cases of reticulosis were studied. One patient with lymphadenoma who survived had a ChE level of 1·10, while two whose ChE levels were 0·15 and 0·45, died shortly afterwards from lymphadenoma and reticulosis.

POST-HEPATIC JAUNDICE.—Observations were made in 58 patients who had jaundice of post-hepatic origin. The results are given in Table IV.

In most cases where cholelithiasis was associated with jaundice, ChE levels were normal or high. In these cases, jaundice was due to factors other than a stone in the duct, such as pressure from a swollen cystic gland or localized pancreatitis round the tip of the common duct. However, four patients had values less than the normal range: three had associated pancreatitis and the fourth had a peri-cholecystic abscess due to rupture of a necrotic gall bladder. When jaundice was due to stone in the

TABLE IV
CHOLINESTERASE IN POST-HEPATIC JAUNDICE

| Diagnosis | No. of Cases | Range (Delta *p*H units/hr.) | Mean |
|---|---|---|---|
| Cholelithiasis | 15 | 0·36 to 1·91 | 1·08 |
| Stone in common bile duct | 18 | 0·37 to 1·45 | 0·88 |
| Biliary carcinoma | 19 | 0·21 to 1·38 | 0·77 |
| Others | 6 | 0·10 to 1·35 | — |
| | 58 | — | 0·87 |

common bile duct, only three out of 18 patients had ChE levels below normal: in two of these, biliary cirrhosis was also present and the third had the added complication of bronchopneumonia. In biliary tract carcinoma, only six out of 19 had levels under the normal range. There were complicating factors in all six: in three, hepatic metastases were present; in two, biliary cirrhosis had developed following long-standing obstruction; and the final case may have had hepatocellular damage from either syphilis or diabetes mellitus, both of which were present.

In the miscellaneous group of six cases of post-hepatic jaundice, subnormal levels of ChE activity (0·26 and 0·10) were observed in two patients with chronic infection, namely pancreatic abscess and subphrenic abscess.

In Fig. 6, the findings in biliary tract carcinoma and stone in the common bile duct are compared with these in 21 cases of hepatic jaundice due to cirrhosis or hepatitis. The cases with ChE levels under normal are ringed to show the presence of the complicating factors mentioned above.

### Prognostic Value of Cholinesterase in Jaundice

In this series, ChE levels of under 0·55 delta *p*H units/hr. were of grave significance in hepatic jaundice as 50% died in hospital. Five out of six patients with levels under 0·15 and nine out of 11 with levels under 0·35 died after brief illnesses. Of the remaining two patients, one had advanced cirrhosis with a gross ascites; the other patient, a young woman aged 26, had a ChE activity of only 0·19 which subsequently fell to 0·03 before she finally died from a continuing chronic hepatitis. Five of the group underwent operation when the ChE activity was under 0·5. All five died in the post-operative period. In the similar group of patients with post-hepatic jaundice and a ChE level of under 0·55 , 11 out of 15 survived.

### Relation to Level of Plasma Albumin in the Presence of Jaundice

ChE activity has been related to the level of circulating plasma albumin in 67 jaundiced patients. In 12 patients where the albumin level lay between 2 and 3%, the mean ChE was 0·53, rising to 0·78 in 45 patients where the albumin was between 3 and 4%. In 10 patients with plasma albumin over 4% the ChE mean was 0·92. In general, ChE activity followed the level of plasma albumin, low levels being found when the concentration of albumin was reduced and vice versa. However, there were many individual cases where there was no clear relationship. ChE activity was subnormal in seven out of 12 patients (58%) whose plasma albumin was under 3% and in 21 out of 55 (38%) in the group with albumin levels over 3%.

The following points are worthy of note in the five cases where a normal ChE was associated with a plasma albumin level of under 3%. In one case, ChE was at the lower level of normal. A fall may well have occurred from a more normal level as the patient's condition deteriorated with the development of jaundice complicating cirrhosis. In a further two cases, although apparently normal at the time of comparison with albumin, ChE activity had fallen by 52% in one case and in the other subsequently fell by 49%, in both cases showing the reactivity of the test to infection. Only in two cases was there no apparent explanation for the low albumin level in conditions where the ChE would not be expected to be low. On the other hand, ChE was subnormal in 21 cases in the presence of albumin at a concentration over 3%. In 11 of these cases a hepatic cause of the jaundice was present: in the remaining 10 where the jaundice was of post-hepatic origin there was in nine a reasonable explanation for the low ChE levels, namely, cholangitis, hepatic metastases, or secondary biliary cirrhosis.

Relation to Depth of Jaundice.—ChE activity has been compared with the depth of jaundice present in 79 patients, using serum bilirubin as an index of the intensity of jaundice. The results are summarized in Table V. ChE activity was found to be low in those patients who were deeply jaundiced. This finding is of little diagnostic significance as the lesions responsible for the jaundice in patients with serum bilirubin levels over 10 mg.% were those which have been shown to be associated with low ChE activity without reference to the depth of jaundice (cirrhosis in relapse, biliary carcinoma with hepatic metastases, etc.).

TABLE V

RELATION BETWEEN SERUM CHOLINESTERASE AND SERUM BILIRUBIN

| No. of Patients | Serum Bilirubin (mg. %) | ChE Mean | % Under Normal |
|---|---|---|---|
| 57 | Under 10 | 0·83 | 38 |
| 15 | 10-20 | 0·69 | 53 |
| 7 | Over 20 | 0·25 | 86 |

### Discussion

It has been shown that the level of ChE falls in a variety of circumstances not associated with a primary parenchymal lesion in the liver. It falls during the first week after trauma such as surgical

operation or fracture of the femur, and also during *x*-ray therapy but is delayed until the second or third week. A fall has also been demonstrated in severe acute abdominal disease, when complicated by marked infection. Prolonged infection other than abdominal also leads to a fall. It has also been shown that although normal levels of ChE activity vary widely, each individual retains his own level under normal circumstances. On this basis the observed changes in conditions other than hepatic disease would appear to be significant, but there is no clear explantaion for their occurrence.

The post-operative results, considered alone, suggest that liver function is depressed post-operatively, most marked about the fifth day, and that ChE is a sensitive indicator. The positive cephalin cholesterol flocculation results add support to this, but were found only when complicating factors were present. A stronger support for the concept of hepatic injury is the finding of an increase in the output of urinary urobilinogen at the time that a fall in ChE activity was occurring. This was seen even in minor cases. A possible explanation is that hepatocellular injury was interfering with the destruction or re-excretion of urobilinogen absorbed from the intestine in the enterohepatic circulation.

ChE appears to originate in the liver and to be closely associated with the synthesis of serum albumin (Faber, 1943; Kunkel and Ward, 1947; Vorhaus and Kark, 1953). A fall, therefore, may be due to interference with this process in the liver cell. However, the observed post-operative fall may be related to several other factors: (1) Lack of essential amino-acids for its synthesis due to reduced intake in the post-operative phase; (2) loss of plasma protein by exudation at the site of operation, greater than can be currently replaced; (3) dilution of ChE in the circulating plasma during the period of fluid changes occurring in the extracellular space after operation.

In many of those cases which showed post-operative falls of ChE, protein starvation was not a factor, as normal diet was resumed on the first post-operative day. Again, exudative loss at the operation site seems unlikely as operation was uncomplicated in many cases, a restricted site was involved, and post-operative progress was smooth. Dilution appears to be unlikely, as the levels fell post-operatively even after minor procedures.

Another factor of importance in the effect of trauma, operation, and infection on serum ChE levels is increased urinary nitrogen excretion. This may originate in increased catabolism which follows operation and is closely associated with operative trauma as suggested by Wilkinson, Billing, Nagy, and Stewart (1950). On the other hand, ingested protein may be used after injury to supply calories, the nitrogen content being excreted in the urine. Even though the post-operative caloric intake is apparently reasonable, it may not supply all needs. Armstrong (1957) has suggested that, for an average man, 4,000 calories may not be an excessive daily amount following major surgery. The combination of catabolism of body protein for caloric requirements with subsequent excretion of nitrogen could account for the drop in ChE after fracture, after operation, and in infection prolonged for any length of time. A significant change could be seen even in a week as ChE has been shown to have a life span of 28 days (Wescoe, Hunt, Riker, and Litt, 1947).

In the group of cases treated by *x*-ray therapy, the fall did not occur until significantly later—in the second or third week. In these patients, the hepatic area was included to some extent in the field of radiation, and hepatocellular damage due to the *x* rays might be expected to result in the fall which was observed. Alternatively, the synthesis of ChE in the liver might have been impaired by some circulating product of cellular destruction. The lateness of the fall may have been due to the liberation into the blood stream of large amounts of ChE from the store in the liver parenchyma, thus concealing for an interval of one to two weeks the fall due to impaired synthesis of new ChE by the damaged cells. The association of a falling ChE with the symptoms of radiation sickness is of interest in view of the part possibly played by ChE in destroying cholinergic proteoses absorbed from the intestine and perhaps other sites (Barnard, 1952).

In other conditions, several factors may be involved. In haemorrhagic pancreatitis, for example, the observed fall in ChE activity may be the result of various influences in protein metabolism such as reduced intake of amino-acids, increased protein catabolism, and loss of protein by exudation into the site.

Whatever may be its value as an indicator of hepatocellular dysfunction, from the above considerations it appears that measurement of ChE activity can act as a general indicator of protein metabolism in the body. Under normal conditions the level remains constant. It falls in any condition, such as trauma, operation, or infection, which gives rise to increased catabolism; it rises subsequently to normal levels in the anabolic phase as in the healing stage of a fracture.

Estimation of ChE activity can be used as a liver function test in two different ways: as an index of liver function and as an aid in the differential diagnosis of jaundice. If a patient is known to have

hepatic disease, ChE activity of less than the lower limit of normal (0·55 delta *p*H units/hr.) is indicative of serious disease. It follows that in conditions where hepatic disease is suspected, succinylcholine should not be given as a relaxant during anaesthesia unless the level of ChE is known, as ChE is responsible for the destruction of this substance. If the ChE level is under 0·35 the condition of the patient must be regarded as grave, and under no circumstances should he be subjected to operation. On the other hand, in jaundice due to biliary disease, low values of ChE do not carry the same grave prognosis, unless due to secondary carcinoma of the liver. In the remaining cases, low values are due to chronic infections such as cholangitis and pancreatic abscess, or to biliary cirrhosis without such other evidence of hepatocellular injury.

The low values seen in secondary carcinoma have been ascribed to cachexia, but Fremont-Smith, Volwiler, and Wood (1952) found a depression of ChE in the absence of cachexia. This is confirmed in the 24 cases in this investigation where cachexia was present only in the minority. Fremont-Smith and his co-workers found no difference between the mean value of ChE in patients cachectic from carcinoma, and the mean value in a series of patients suffering from extreme malnutrition due to other causes. It has been suggested that the low values in patients with liver metastases might be due to a local effect of the tumour on ChE formation by the liver cell (Williams, La Motta, and Wetstone, 1957). Another possible explanation is that the sheer bulk of the active tumour cells may utilize such a large amount of available nitrogenous material that the host is left with insufficient to continue with normal anabolic processes such as the formation of albumin and ChE (Terepka and Waterhouse, 1956).

The use of ChE activity as a test in the differential diagnosis of jaundice is limited by the response of the ChE to general metabolic changes, not necessarily associated with specific hepato-biliary disease. If some of the general factors previously discussed, such as chronic infection or operation, were to be introduced into a case of jaundice, great care would be required in interpretation of the ChE levels. An additional hazard is the development of secondary hepatic damage in patients who have a post-hepatic jaundice. It has been shown that secondary biliary cirrhosis due to chronic biliary tract obstruction and the presence of liver secondaries from biliary tract carcinoma will be associated with ChE activity of "hepatic levels". The diagnostic value of ChE is thus impaired to some extent. Nevertheless, levels under 0·35 have been found to be rare in post-hepatic jaundice unless obvious infection such as subphrenic abscess or pancreatic abscess is present. Measuring the activity of ChE should never be used by itself as a diagnostic test in jaundice. If used in combination with other tests which suggest hepatic disease, a low value will substantiate this. An extremely low value indicates a grave prognosis and operation should be avoided. A normal level, if borne out by clinical diagnosis and other function tests, will support the diagnosis of post-hepatic jaundice. If there is strong evidence that biliary tract carcinoma is present, a level under the lower limit of normal is an indication of secondary liver cell damage or of the presence of hepatic metastases.

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# SERUM ALBUMIN, PSEUDOCHOLINESTERASE, AND TRANSAMINASES IN THE ASSESSMENT OF LIVER FUNCTION BEFORE AND AFTER VENOUS SHUNT OPERATIONS*

BY

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This paper records biochemical and follow-up observations on 153 patients with cirrhosis who have had a shunt operation. The experience confirms that no shunt operation should be undertaken on a patient whose serum albumin level is less than 3·2 g.%. Low pseudocholinesterase levels are of help diagnostically but the main value of this test is in indicating whether or not liver function will deteriorate after a shunt operation in any given patient.

The selection of cirrhotic patients for porta-caval anastomosis is a complex matter, since only a proportion of those for whom operation is indicated are suitable. The indications for operation are clinical, in that the operations are designed to prevent or to stop haemorrhage from gastro-oesophageal varices, to reduce or to neutralize the anaemia, etc., of an overactive spleen, and, occasionally, to relieve ascites. The means of achieving the desired effect on the portal circulation is to divert portal blood directly into the systemic circulation and, of necessity, away from the liver. It is, therefore, essential for the patients to have a certain minimum reserve of liver function so that they will not die of liver failure during the immediate post-operative phase. It is then to be hoped that the liver function will be maintained over the years that follow so that the patients will be able to lead normal lives and continue at work.

The purpose of this communication is to relate the findings of certain tests of liver function to the clinical results obtained in a group of patients operated on before October, 1959, and to evaluate them as a means of assessing the prognosis of a patient about to undergo a shunt operation. In this context, diagnostic tests of liver disease are no more than adjuvant, as indeed are tests of biliary obstruction and the capacity of the liver to eliminate bromsulphthaleine and to form prothrombin. We do not wish to minimize in any way the importance of these tests and other means of estimating how much of a specific liver function remains or the extent of its derangement. We realized early in our studies that the tests which would serve us best in the assessment of prognosis would be those which would give a direct estimation of the function of the liver as reflected by its capacity to manufacture substances vital to the metabolism of the organism as a whole. Two serum components, albumin and pseudocholinesterase, are just such substances. They are made by the liver and their concentration indicates how much normal liver function is present. Malnutrition, haemodilution, and variations in the normal values must be allowed for in the evaluation.

We also realized that many patients died because their liver disease continued to progress. At no time has it been pretended that a surgical procedure could arrest such a degenerative process. Recently we have been investigating the serum glutamic-oxalacetic and glutamic-pyruvic transaminases, in the hope that they might show how much active disease was present within the liver at the time a shunt operation was done and possibly indicate those patients in whom deterioration might be expected, they having survived the porta-caval anastomosis.

## Serum Albumin

Up to the end of 1954 albumin was estimated by the biuret method after precipitation of the globulins by half-saturation with ammonium sulphate (Harrison, 1937). From 1955, globulin precipitation after Kingsley's method with ether and sodium sulphate was used (Hawk, Oser, and Summerson, 1947). The lower level of normal was considered

* Based on a paper read to the joint meeting of the Association of Clinical Pathologists and the Association of Clinical Biochemists on October 3, 1959.

to be 3·5 g. per 100 ml. of serum. Differences in results of duplicate estimations or of estimations done on the same serum on different days did not exceed 0·1 g. albumin per 100 ml. serum.

The level of serum albumin has for some time been recognized to be of prognostic value. Blakemore as long ago as 1949 was emphatic in his opinion that shunt operations should not be undertaken on patients with serum albumin levels of less than 3·2 g. per 100 ml. We do not attach undue importance to a single laboratory figure to the exclusion of more empirical and less easily defined clinical methods of assessment, but we agree in general with Blakemore's opinion, provided the estimation is carried out reliably, recognizing that standards vary from one laboratory to another. This one test, above all others, helps in the selection of patients likely to survive the shunt operation itself. After that, some patients do well, some deteriorate and ultimately die, and in some the clinical course fluctuates. The pre-operative serum albumin level gives disappointingly little indication of those patients in whom the liver will ultimately fail.

### Pseudocholinesterase

Our attention was drawn to this test in 1952 by the late Professor Bruno Mendel, of the University of Amsterdam, who suggested that it might prove valuable as a prognostic test complementary to the serum albumin. The method of estimation has throughout been that of Jones and Tod (1935) and McArdle (1940). It depends on the measurement in a Warburg micromanometer of the amount of $CO_2$ liberated when acetylcholine is added to a mixture of serum and Krebs-Ringer bicarbonate buffer.

The esterase hydrolyses acetylcholine into choline and acetic acid, and the acid liberates $CO_2$ from bicarbonate. Results are expressed in c.mm. (units) of $CO_2$ liberated by 1 ml. of serum in one minute at 37°C. Measurements are made in duplicate and do not differ by more than 6 units. The mean of the two results is recorded.

In a series of 100 adults without disease values varied from 65 to 124 units. For practical purposes only values under 55 units were considered abnormal. We have come to realize, while making due allowance for the wide range that exists between individuals, that there is a critical level of 30 to 35 units. The interpretation of single measurements has been complicated by the finding of a rare genetically determined pseudocholinesterase deficiency which is unrelated to liver disease or malnutrition. All homozygotes and a proportion of the heteroyzgotes for the abnormal gene show values below 55 units (Lehmann and Ryan, 1956; Lehmann, Patston, and Ryan, 1958). Kalow and his colleagues (Kalow and Genest, 1957; Kalow and Gunn, 1959) have shown that such low pseudocholinesterase values are associated with an atypical enzyme which has a low affinity for acetylocholine. Harris, Whittaker, Lehmann, and Silk (1960) have examined 58 immediate relatives of 11 homozygotes for the abnormal gene and have confirmed that homo- and heterozygotes can be recognized from tests demonstrating the atypical pseudocholinesterase. It is, therefore, possible to show whether a low pseudocholinesterase level is due to a fall in the concentration of the normal enzyme or due to full or partial replacement by the genetically determined atypical esterase.

### Serum Transaminases

The glutamic-oxalacetic and the glutamic-pyruvic transaminases were determined by the method of King (1958) and Reitman and Frankel (1957) using a routine photoelectric colorimeter with a green filter (Lehmann and Ryan, 1957). Whereas serum albumin and serum pseudocholinesterase are made by the liver and their concentration is a direct outcome of liver function, concentrations of serum transaminases are raised when liver cells are destroyed. The liver is by no means the only organ from which transaminases can be liberated when cell damage occurs. Abnormal transaminase levels must, therefore, always be considered in conjunction with other tests and with the clinical picture. When necrotic heart or skeletal muscle cells are the source of the serum transaminases, the level of the serum glutamicpyruvic transaminase is either normal or, if raised, well below that of the serum glutamic-oxalacetic transaminase (Wroblewski and LaDue, 1956a). In liver damage both transaminase concentrations may rise, the serum glutamic-oxalacetic transaminase level is proportionately higher in acute conditions and lower in chronic damage (Wroblewski and LaDue, 1956b). The upper level of normal for both transaminases was taken as 40 units and with careful technique there was no variation in result. If duplicate estimations varied by more than 2 units the estimation was repeated. Extreme accuracy is only needed when the test is used for diagnosis of cardiac infarction and in this study duplicate estimations were not carried out after 1957.

### Clinical Analysis

The analysis deals with 155 cirrhotic patients who have undergone 157 shunt operations between 1948 and October, 1959. The number of patients with cirrhosis of all types seen during this period was 347. Shunt operations were not done in more than half, either because there was no clinical indication, *e.g.*, satisfactory response to medical treatment for

ascites; cirrhosis discovered incidentally as disease associated with peptic ulcer, etc., or because they were too ill for operative treatment.

The subdivision into mild, moderate, and severe cirrhosis was arbitrary (Hunt, 1958), designed only to indicate roughly how the patients would be expected to react to any major operation; the mild at little and the moderate at reasonable risk, but the severe at considerable danger. Many physicians have cooperated with us at every point and we are most grateful to them for their help. All modern methods of medical treatment have been used as they have been introduced.

## Results

The results have been assessed as follows.

"Success" means that a patient has been restored to normal life and work, without haemorrhage or ascites, indicating that portal hypertension has been relieved and liver function maintained. Death occurring from an intercurrent disease, *e.g.*, carcinoma of bronchus, has not altered a previous decision to call the case a success, nor have mild and transient and controllable attacks of episodic stupor. The results recorded here are appreciably better than those recorded in 1958.

"Late post-operative deterioration" infers that the patient recovered from the operation and later went downhill. Many have succumbed from liver failure, often preceded by attacks of episodic stupor. However, a proportion of the patients falling into this group were able to lead normal, useful, and happy lives for months or even years, in spite of diminishing liver function. In this sense the operation itself must be considered successful in that the risk of haemorrhage was removed and ascites eliminated, though the operation had done nothing to delay the progression of the liver disease. The terminal deterioration in such cases is often precipitated by an intercurrent disease, or some intervention of no greater severity than dental extractions. In this group are included those whose shunts have thrombosed and in whom the operation was of no benefit, though the patients survived.

"Post-operative deaths" include all patients dying in hospital following operations and those dying of complications resulting from the operation itself. We recognize that the death rate among early cases, certainly before 1951, was higher than it is today because our methods of selection were faulty and the patients were not, according to our present standards, always fully prepared, nor was our operative technique so practised, nor were our methods of pre- and post-operative treatment so effective or precise.

Lastly, it must be remembered that a patient with cirrhosis has not the ability to resist intercurrent disease that is possessed by those fortunate enough to have normal livers, especially if an active parenchymatous lesion is present. Operations are undertaken, and indeed their whole lives are lived at added risk.

### Method of Tabulating Results

The following graphs, Figs. 1, 2a and b, 3a and b, show the serum albumin and pseudocholinesterase levels for the three groups of patients: the mild, the moderate, and the severe cirrhotics. The graphs were compiled from figures obtained by taking the average reading for each patient over a particular period, the pre-operative phase and during each year post-operatively. Excluded from the analysis were the especially low readings encountered after a severe haemorrhage or during the immediate post-operative phase. The number of cases from which the readings were obtained is recorded for each period (the figure below the lower limit of variation for each period), but it may be short of the number of patients followed up through that particular year because the graphs do not take account of the patients who work abroad and can only attend for follow-up at irregular intervals. Each figure may, however, represent the average of a considerable number of readings, especially during the first post-operative year when the liver function tests may be repeated at two- or three-monthly intervals. The average, the highest, and the lowest figures are recorded.

The graphs were originally compiled as scattergrams, but the mass of detail was such as to confuse the issue. In the simplified form in which they are presented, clarity has been obtained at the expense of emphasizing the variations above and below the normal for each group of patients. It is, however, only the exceptional case that falls far wide of the average. Occasionally, in the assessment of a patient, the translation of a reading from "a statistic" into a figure of unique importance for an individual becomes a matter of some difficulty, but it must be borne in mind that it is only in this article that we are emphasizing certain biochemical tests. Much other material evidence—clinical, biochemical, and radiological—is normally considered in deciding the course to be adopted for a particular patient.

The Mild Cirrhotics.—These are patients who do not show any material evidence of hepatic disease pre-operatively and whose liver functions are within normal limits. Twenty-four out of 27 could be genuinely classified as long-term successes, giving a total of 89% success. There was no post-operative death. The liver function has remained normal during the whole period during which these patients have been

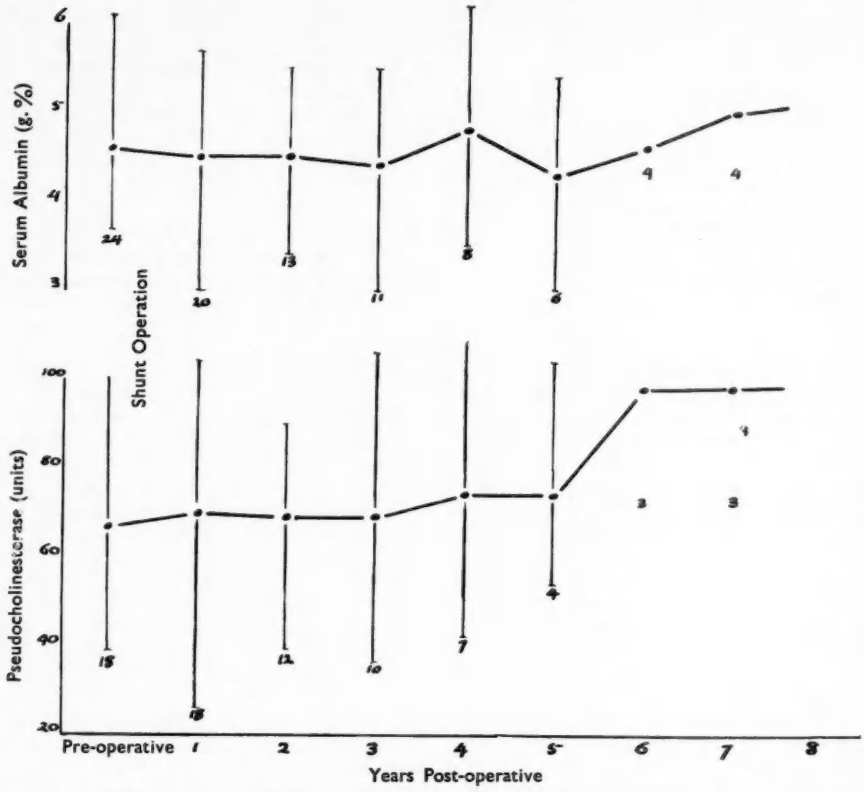



FIG. 1.—*Serum albumin and pseudocholinesterase levels in 24 mild cirrhotics who have undergone successful operation for porta-caval or lieno-renal anastomosis. There is a tendency for the liver function, which is good pre-operatively, to improve post-operatively over the years.*

under observation (up to more than 10 years), the serum albumin at 4·5 g.% (4·6 g.% pre-operatively) and the pseudocholinesterase at 70 (Warburg) units (67 units pre-operatively) (Fig. 1).

THE MODERATE CIRRHOTICS.—These are patients who show evidence of liver disease clinically or on biochemical assessment, but whose condition is not in the first place so severe as to preclude a shunt operation. They numbered 88; 56 have been successfully operated on and 22 have deteriorated over the years, but in 17 of these the porta-caval anastomosis benefited them, giving a total of 83% materially improved by the anastomosis. Post-operative deaths numbered 10 (11%).

In the successful group (Fig. 2a) the serum albumin pre-operatively was 4·4 g.% and during the first four to five years since operation has not, on average, dropped below 4·1 g.%. The pseudocholinesterase, 60 units pre-operatively, has fluctuated during the four years between 58 and 64 units. The picture is much the same as for mild cirrhosis, though on a slightly lower level.

In those who deteriorated (Fig. 2b) the serum albumin pre-operatively was 4·3 g.%, almost identical with the former group, but it did, on average, sink to 3·5 g.% before terminal deterioration. The pseudocholinesterase, 49 units pre-operatively (11 units less than the successful group), fell off rapidly to 32 units.

Of the 10 who died post-operatively, the pre-operative serum albumin was 4·1 g.% and the pseudocholinesterase 70 units. Death, on the whole, was not related to any deficiency in liver function, but to a number of other matters, of which technical difficulties played a considerable part.

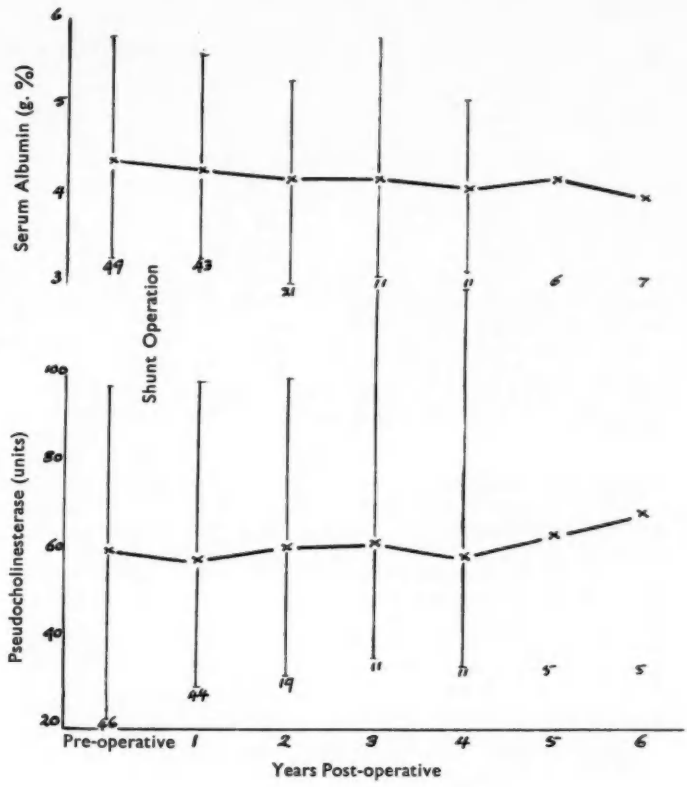
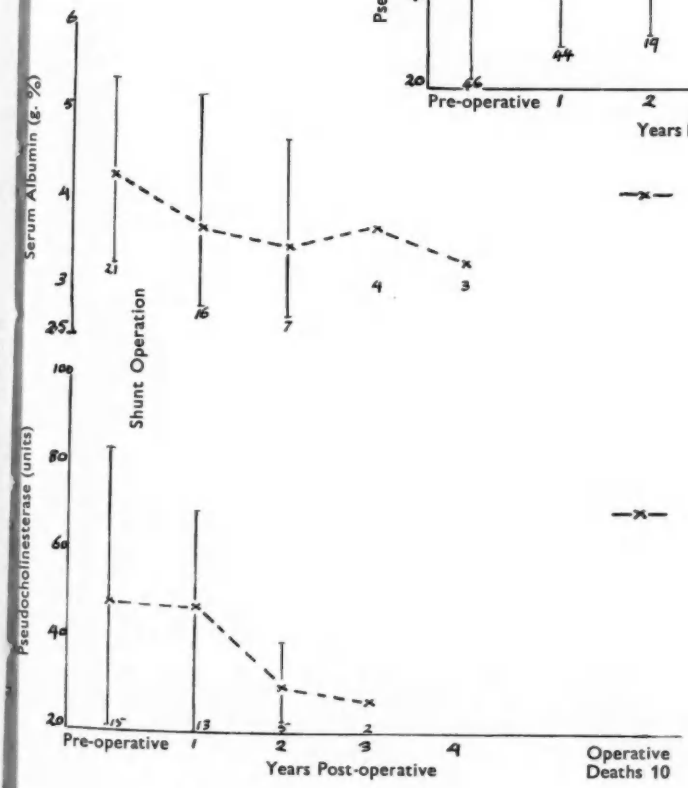



FIG. 2.—*Serum albumin and pseudocholinesterase levels in moderately cirrhotic patients: A, 56 patients who have had a successful shunt operation and in whom the liver function is maintained; B, 22 patients in whom there has been deterioration of liver function post-operatively. (The pre-operative pseudocholinesterase level in B is disproportionately low.)*



It will be noted that although the pre-operative level of serum albumin in moderate cirrhosis is the same in the groups that do well and in those that do badly, the average level of pseudocholinesterase is appreciably lower in the second group. A glance at the graphs will make it obvious that the assessment of an individual patient is a difficult matter because of the wide variations in the level of pseudocholinesterase. However, a low level or a change for the worse is undoubtedly a pointer towards ultimate liver failure. This is shown well during the second year of follow-up in the patients who deteriorated. At a time when the average serum albumin dropped only 0·2 g.% (from 3·7 to 3·5 g.%), the pseudocholinesterase fell from 48 to 32 units.

THE ADVANCED CIRRHOTICS.—These are the patients who, when first seen, were considered too ill to tolerate a shunt operation on account of the advanced state of their liver disease, sometimes related to serious illness affecting other vital organs. Most patients in this group never improved sufficiently for a definitive operation to be undertaken. With intensive medical treatment lasting at least three and sometimes for 10 months, 40 attained a state in which a shunt operation was deemed justifiable. The serum albumin in nine patients rose during the pre-operative phase from an average of 2·5 g.% to an average of 3·8 g.%.

Twenty-one (52·5%) did well (Fig. 3a). Over the first three post-operative years the serum albumin has fluctuated between 3·8 and 4 g.% and the pseudocholinesterase, 46 units pre-operatively, has improved to between 56 and 58 units during the same period.

It is only coincidence that the level of 46 units in this group of advanced cirrhotics who do well is identical with the level in the group of moderate cirrhotics who do badly, illustrating the point that most of the biochemical tests of liver function must be evaluated in relation to the clinical state of the individual. The serum albumin provides the absolute standard of comparison; the pseudocholinesterase indicates a trend.

The findings in this group suggest that if a patient responds well to medical treatment pre-operatively, the prognosis is good. Some of the patients who have done best of all have required many months of intensive medical treatment before reaching a state at which the risk of operation has been justified. The figures in this group prove beyond shadow of doubt that liver function may actually improve following shunt operations and that prolonged and persistent pre-operative treatment in an apparently hopeless case sometimes pays excellent dividends.

Seven advanced cirrhotics have deteriorated post-operatively (Fig. 3b), but four were temporarily improved, so that one can say that altogether in 25 (or 62%) a shunt operation has been of great value. Pre-operatively the average serum albumin level was 3·8 g.% (identical with the successful group) and the pseudocholinesterase 36 units (10 units less, be it noted again, than in the successful group).

In the advanced cirrhotics who died post-operatively (Fig. 3b), the serum albumin level averaged 3·5 g.% pre-operatively and the pseudocholinesterase 36 units. They number 12 and constitute 30% of this very ill group. However, many of these patients had not been considered fit for operation by other surgeons interested in portal hypertension and most had only attained a reasonable state after prolonged and intensive medical treatment. Many would never have been included in other surgical series so the unduly high operative mortality in this group must be viewed in correct perspective. At the expense of a 30% operative mortality, much has been gained for those patients who have survived.

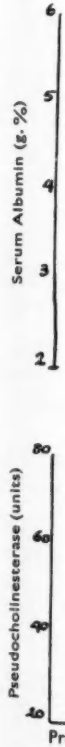
ALL GROUPS.—Fig. 4 has been drawn to emphasize the significance of the results of Figs. 1, 2, and 3. The proportionately lower placement by 10 or 11 units of the pseudocholinesterase levels pre-operatively in those patients who ultimately die becomes more evident. The serum albumin in each group (related to the degree of cirrhosis) is by contrast the same.

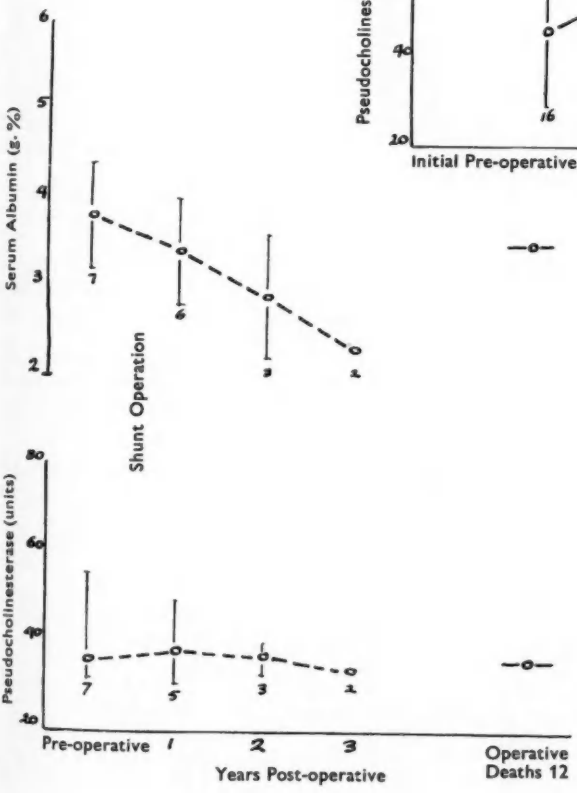
The advanced group contains most of the ascitic patients. Usually they have also had haemorrhages and some were jaundiced. It is often said that ascites and jaundice are contraindications to shunt operations, but this is not necessarily so, provided the liver function recovers reasonably well, as indicated by the serum albumin rising to above 3·2 g.% and pseudocholinesterase levels improving.

Altogether 35 patients have had gross ascites at the time of their portal-systemic venous anastomosis (reported by Knipe, 1959). All who survived operation have been temporarily or permanently relieved of ascites and 25 have been enabled to return to full work or normal life (71%). Clinically the prospects of a patient with intractable ascites, which has failed to respond to medical treatment, are bad; but we think that we can, by these biochemical tests, select those patients who may be expected to benefit from operative treatment.

## TRANSAMINASES

So far in this analysis we have dealt with the two tests which we consider to be particularly valuable in assessing prognosis. This does not infer that we





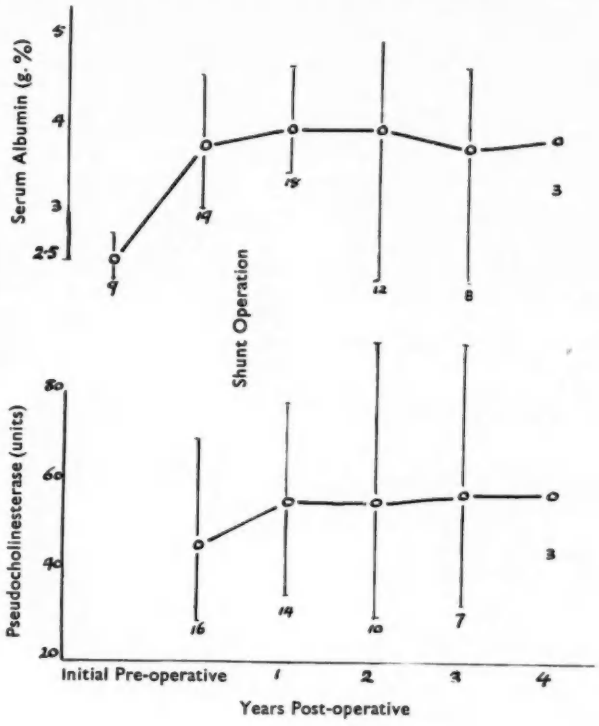




FIG. 3—*Serum albumin and pseudocholinesterase levels in patients with advanced cirrhosis. A, in* 21 *patients before and after successful shunt operation, with liver function well maintained; B, in seven patients when there has been ultimate liver failure. Again, the pre-operative pseudocholinesterase level in B is disproportionately low.*

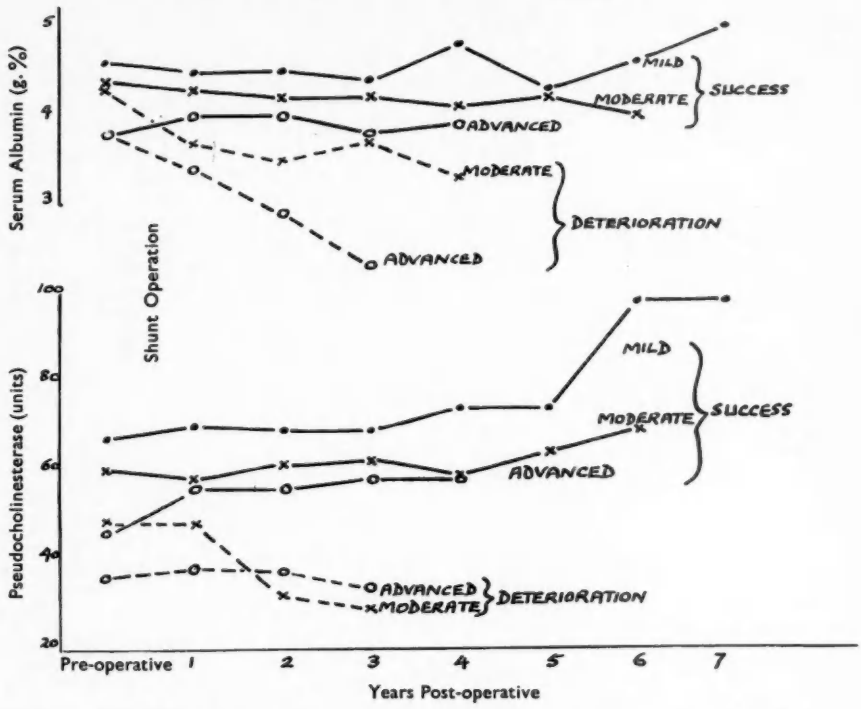



FIG. 4.—*Composite graph emphasizing the prognostic value of pseudocholinesterase in the pre-operative assessment of patients with moderate and advanced cirrhosis.*

have restricted our biochemical investigations of liver disease to these two tests alone. We use many others when we feel they are indicated. Recently we have been investigating the serum glutamic-oxalacetic and glutamic-pyruvic transaminases in the hope that they would indicate the continued activity of a pathological process within the liver and thereby warn us of an unfavourable circumstance. So far, however, we have not been able to come to a definite conclusion about their value, because the levels have varied greatly and a raised transaminase level does not necessarily indicate an overall incapacity of the liver to carry out reasonable function; nor is a "normal" level or a fall in the transaminase level invariably an indication that no destruction of liver cells is going on, or that the pathological process is regressing. So many of the cells may have been destroyed already that the remainder, though injured, do not contribute much enzyme to the serum. In such patients a fall in the transaminase levels may be a bad rather than a good sign, especially if associated with a fall in the pseudocholinesterase level. Transaminase activity should therefore, be considered in conjunction with other tests.

The average levels have been as follows:

| | | Pre-operative | | Post-operative |
|---|---|---|---|---|
| *Mild cirrhosis* | S.G.-O.T. | 31 | | 30 |
| (5) | S.G.-P.T. | 28 | | 21 |
| *Moderate* | S.G.-O.T. | 96·5 | Elevated | 67 |
| (good results, 20) | S.G.-P.T. | 63 | | 43 |
| *Moderate* | S.G.-O.T. | 35 | Normal | 66 |
| (poor results, 6) | S.G.-P.T. | 24 | | 37 |
| *Severe* | S.G.-O.T. | 80·5 | Elevated | 82·5 |
| (good results, 8) | S.G.-P.T. | 63·5 | | 38 |

We may be able in time to detect the likelihood of improvement or deterioration as judged by the degree of activity. Two successful cases illustrate this hope.

The first, a boy with congenital cystic disease of the pancreas, cirrhosis, and bronchiectasis, showed the following fluctuations in transaminase: S.G.-O.T. pre-operatively 160, improving to 55 with medical treatment, deteriorating to 135 post-operatively, and then improving to 58 units; S.G.-P.T. pre-operatively 110, improving to 58,

deteriorating to 80 post-operatively, and then improving to 17 units. The boy is doing well 19 months after operation.

The second, a man with gross ascites and haemorrhage, who has done extraordinarily well, showed the following improvement during three months' pre-operative treatment: S.G.-O.T. 30 to 14 units, S.G.-P.T. 48 to 22 units.

## Conclusion

In studying the problem of liver disease from a surgical point of view, there is need for a test (or group of tests) which will enable us to distinguish clearly in the individual pre-operatively the patient who will not only tolerate a shunt operation but also not deteriorate later. That no such test has as yet been available may be a blessing in disguise, in that hope has not yet to be withheld from the patient who will ultimately deteriorate. A shunt in such circumstances may bring much relief and even great happiness, even though life may not be prolonged beyond a few years, but these are lived without the threat of devastating haemorrhage and the discomfort of incapacitating ascites. The serum pseudocholinesterase, we believe, gives us prior information of value and follow-up estimations show what the clinical trend will be in advance of other findings. It also responds much more rapidly to day-to-day changes in the state of the liver. Taken in conjunction with the serum albumin, its estimation is, therefore, of great value. Further, it must not be forgotten that a level of less than 55 units is almost certainly diagnostic of liver disease, whatever the other tests show. We are led to the emphatic conclusion that, in our experience, the serum albumin and serum pseudocholinesterase levels are the two most important estimations in helping to assess the prognosis of a case of cirrhosis before operation and during the follow-up period. The whole subject, however, of portal hypertension is of such complexity that the biochemical laboratory can be no more than ancillary and we fully recognize that clinical appraisal is at least as important as any or all the liver function tests.

## Summary

One hundred and fifty-five patients with cirrhosis, in whom shunt operations have been done, have been analysed in order to relate the clinical outcome on the one hand to the extent of the cirrhosis on the other, the liver function being assessed by estimation of the serum albumin and pseudocholinesterase levels.

The serum albumin gives, on the whole, an accurate assessment of the overall liver function. We confirm that no shunt operation should be undertaken in a patient whose serum albumin is less than 3·2 g.%.

The pseudocholinesterase level is of supplementary value and, although the range of normal values is wide, it appears that 30-35 units is a critical level. Low readings are of value diagnostically, but the most important assistance to be derived from the pseudocholinesterase is that it gives an indication of whether or not the patient will undergo late deterioration of liver function after a shunt operation. A material falling off in the pseudocholinesterase level is seen before the serum albumin alters significantly. Day-to-day changes are sometimes reflected by this test.

An assessment of the transaminases is not yet possible, but it appears that they will have to be evaluated in conjunction with the other tests of liver function so that the amount of enzyme liberated is related approximately to the total quantity of functional liver substance present.

The analysis has shown conclusively that liver function may not only be maintained for years following a shunt operation but that it may actually improve. The methods of assessment described in this article go part of the way to indicating, before operation, what the ultimate result will be. A shunt operation has proved successful or worthwhile in 87% of the mild cirrhotics and in 83% of the moderate cirrhotics. Even in the advanced cirrhotics, a group of patients normally precluded from this operation, a proportion become suitable for a shunt and of these 62% have done well.

We should like to thank Mr. H. F. Weston who supervised the estimation of nearly all albumin values, and Mrs. E. Silk, Mrs. H. Kay, Miss E. Ryan, and Miss V. Patston who as research assistants carried out estimations of pseudocholinesterase. We should like to thank the Medical Research Council who provided a research assistant from 1951 to 1954 and the Governors of St. Bartholomew's Hospital who continued this financial support from 1954 to 1959.

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# ANEURYSM OF THE SPLENIC ARTERY

BY

P. D. BEDFORD and BRIAN LODGE

*From the Cowley Road Hospital, Oxford*

This paper records an incidence of 10·4% of aneurysm of the splenic artery in 250 consecutive routine post-mortem examinations. Medial degeneration seemed to be the commonest cause of such aneurysms and although a number were associated with other intraabdominal pathology, including portal hypertension, the association may be fortuitous and not causal.

Aneurysm of the splenic artery was first reported by Beaussier (1770). This and the second case reported by Parker (1844a and b) were for many years omitted from the literature and priority mistakenly given to Crisp (1847) by all subsequent authors, possibly because he himself had also erroneously credited Parker with the description of the first case.

The subject was last extensively reviewed by Owens and Coffey (1953) who found 198 cases described in the literature and added six more of their own. They mentioned an additional 12 cases, of which reports were too vague for them to include and a further 21 cases mentioned *en passant* in necropsy surveys, making a total altogether of 237 cases. A further 18 cases described since their review, together with seven cases of Turnbull (1915) which all previous surveys have curiously failed to include, brings the total in the world's literature to 262. The literature is largely made up of reports of a few cases derived incidentally from retrospective studies of large routine necropsy series and recorded often with little comment as rarities, or of clinical reports of either single cases or small groups of cases.

This communication seeks to establish that aneurysm of the splenic artery, far from being a rarity, is on the contrary a common condition. It sets out to explain how this fallacy has probably arisen; and to propose, in the light of the new evidence adduced, a revision of some widely held and generally accepted views and beliefs regarding the aetiology and treatment of the condition.

A comprehensive bibliography has been appended, including references to all previously recorded cases of aneurysm of the splenic artery.

## Source of Data and Method

Following the chance discovery at necropsy of an unsuspected aneurysm of the splenic artery, a special study of the vessel was made in a consecutive series of 250 routine necropsies on patients dying at the Geriatric Unit, Cowley Road Hospital, Oxford.

The series comprises 108 males and 142 females, whose ages ranged respectively from 34 to 100 years (average 72) and 31 to 99 years (average 77). The distribution by age and sex is shown in Table I. All the patients were under the care of one of the authors; and assessment and morbid anatomical study of all 250 cases was conducted by both personally. The preponderance of females over males in the cases examined simply reflects the greater number of female admissions to this hospital and similar units throughout the country, which in turn reflects the progressively increasing proportion with age of elderly women in the general population in all quinquennia over 65 (*cf.* Registrar General's (1959) Statistical Review of England and Wales for 1957).

The method adopted at necropsy was to remove the spleen and pancreas *en bloc* and subsequently to make a complete dissection of the splenic artery. Where an aneurysm was disclosed, the preparation was fixed in 10% formol-saline. Injection of splenic arteries in no case brought to light an aneurysm not already revealed by dissection alone. The post-mortem examination included a careful study of the aorta and of the coronary and cerebral arteries.

## Results

Aneurysm of the splenic artery was found in 26 (eight men and 18 women) of the 250 routine consecutive necropsies, an incidence of 10·4% comprising 7·4% of males (eight out of 108) and 12·9% of females (18 out of 142). All the aneurysms were symptomless and unsuspected and were all therefore quite incidental discoveries. The age of patients with aneurysm ranged from 50 to 80 years (average 71) in the males, and from 48 to 94 years (average 79) in the females (see Table I). Aneurysm of the splenic artery continues to be found at the rate of approximately 1 in 10 of all necropsies carried out in this hospital.

TABLE I
AGE OF PATIENTS

| Age (years) | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80-89 | 90-99 | 100 or over | Totals |
|---|---|---|---|---|---|---|---|---|---|
| Males | 1 | 1 | 10 | 24 | 41 | 26 | 4 | 1 | 108 |
| Aneurysms | 0 | 0 | 1 | 2 | 4 | 1 | 0 | 0 | 8 |
| | — | — | 10% | 8·3% | 9·8% | 4% | — | — | 7·4% |
| Females | 1 | 3 | 13 | 17 | 42 | 48 | 18 | 0 | 142 |
| Aneurysms | 0 | 1 | 0 | 2 | 4 | 7 | 4 | 0 | 18 |
| | — | 33% | — | 11·7% | 9·5% | 14·6% | 22% | — | 12·7% |
| Total (M. and F.) | 2 | 4 | 23 | 41 | 83 | 74 | 22 | 1 | 250 |
| Aneurysms | 0 | 1 | 1 | 4 | 8 | 8 | 4 | 0 | 26 |
| | — | 25% | 4·3% | 9·8% | 9·4% | 10·8% | 18% | — | 10·4% |

ANEURYSMS

| | |
|---|---|
| Overall average age = 76·4 yr. | Male: average age 70·9 range 50-80<br>Female: average age 78·9 range 48-94 |
| 250 necropsies overall average age = 74·9 yr. | Male: average age 72·2 range 34-100<br>Female: average age 76·9 range 31-99 |

Ratio of aneurysms male/female = 7·4%/12·7% = 1 : 1·7.
Ratio of admissions male/female = 2/3 = 1 : 1·5.
Ratio of all deaths male/female = 3/4 = 1 : 1·3.

### REPRESENTATIVE CASE REPORTS

CASE 1 (CRH No. 977).—A man of 50 had for two months complained of complete anorexia with nausea and epigastric pain some 20 minutes after meals. Examination revealed a fixed tender tumour in the epigastrium with multiple nodules in the liver. His blood pressure was 140/90 mm. Hg; the blood Wassermann and Kahn reactions were negative; a barium meal examination confirmed the clinical diagnosis of carcinoma of the stomach. He died 20 days after admission to hospital.

*Necropsy* confirmed the diagnosis made in life. The spleen weighed 150 g. and measured 13 cm. × 8 cm. × 2 cm; a splenunculus 3·5 cm. in diameter was found near the lower pole of the spleen and a saccular aneurysm was present at the first bifurcation of the splenic artery where it gave off branches to the spleen and splenunculus (Fig. 1). The aneurysm was 2·5 cm. in diameter with a smooth surface and was not attached to neighbouring viscera; the splenic artery was 5 mm. in diameter and relatively free from atheroma, but atheromatous plaques were present in the wall of the aneurysm. There was minimal atheroma only of the cerebral arteries and of the aorta. The heart and kidneys were normal. Histology of the aneurysm showed degeneration of the medial coat and the picture of true aneurysm (Turnbull, 1915) of the splenic artery with superadded atheroma (Fig. 2). (As this aneurysm is entirely representative of the findings in all the cases in the present series, further histological details and illustrations will not be given in the other case summaries cited here.)

CASE 3 (CRH No. 872).—A woman of 90 died of a posterior cardiac infarction 11 days after admission to hospital following a coronary thrombosis. Her blood

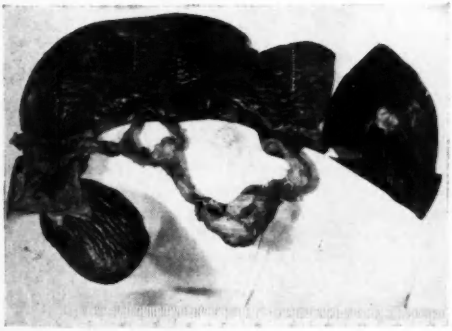

FIG. 1.—*Spleen and splenunculus showing saccular aneurysm of the splenic artery (Case 1).*

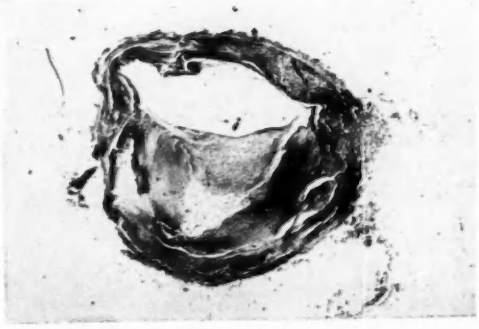

FIG. 2.—*Histology of the aneurysm of the splenic artery in Fig. 1 showing medial degeneration with superadded atheroma.*

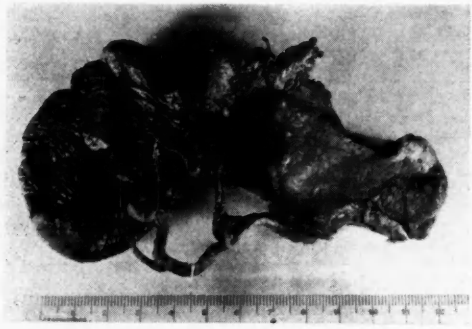

FIG. 3.—*A saccular aneurysm at one of the branches of the splenic artery (Case 3).*

pressure was 180/80 mm. Hg.; the blood Wassermann and Kahn reactions were negative.

*Necropsy* confirmed the diagnosis of myocardial infarction of the posterior wall of the left ventricle, due to thrombosis of the right coronary artery. There was severe atheroma of the thoracic and abdominal aorta and of the cerebral arteries. An aneurysm of the abdominal aorta 2·5 cm × 2·5 cm. × 1 cm. was found immediately distal to the coeliac axis on the left side of the aorta. The heart weighed 225 g. and the spleen 120 g. The spleen measured 7·7 cm. × 5 cm. × 2·5 cm.; there was no splenunculus; the splenic artery was tortuous and heavily atheromatous; an aneurysm 0·8 cm. in diameter was present at the tertiary bifurcation of the vessel (Fig. 3).

CASE 8 (CRH No. 1137).—A man of 66, a known hypertensive for four years, had a first "stroke" six months before his admission to hospital with a second. He was found on examination to have the physical signs of a "supranuclear bulbar palsy". His blood pressure was 250/140 mm. Hg; the ocular fundi showed Grade III hypertensive retinopathy; his urine on routine testing was normal; his blood urea was 30 mg. per 100 ml. and the blood Wassermann and Kahn reactions were negative. He died of bronchopneumonia five weeks later.

*Necropsy* showed bronchopneumonia of the lower lobes of both lungs. The heart weighed 550 g., the left ventricle being grossly hypertrophied; the aorta and the coronary and cerebral arteries were heavily atheromatous. The unfixed brain on section showed multiple zones of old yellow softening scattered throughout both hemispheres and in the brain-stem. The kidneys were shrunken and scarred due to chronic pyelonephritis. The spleen weighed 180 g. and measured 8 cm. × 6 c.n. × 2·5 cm.; there was no splenunculus; an aneurysm 3 mm. in diameter was present at the bifurcation of the lowest (caudal) of the first three branches of the splenic artery (Fig. 4).

FIG. 5.—*Aneurysm of one of the branches of the splenic artery (Case 13).*

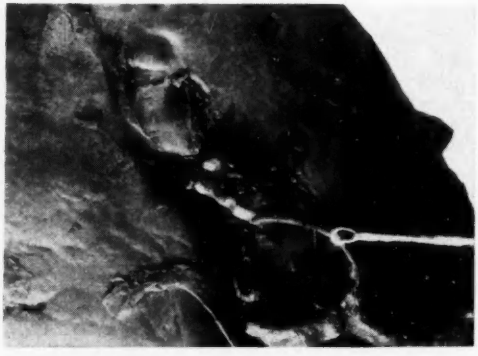

FIG. 4.—*Aneurysm of one of the branches of the splenic artery (Case 8).*

CASE 13. (CRH 986).—A woman of 82 was admitted to hospital with a two-year history of angina of effort. The heart was in sinus rhythm and was grossly enlarged: the blood pressure was 200/110 mm. Hg: the electrocardiogram showed the pattern of a recent anterior myocardial infarction; the blood Wassermann and Kahn reactions were negative. She died in hospital following a second cardiac infarction six months later.

*Necropsy* confirmed the presence of an old anterior and a recent posterior cardiac infarction due to thrombosis of heavily atheromatous coronary arteries. The heart weighed 450 g. There was gross generalized atherosclerosis of all arteries including the aorta, renal, coronary, cerebral, hepatic, and splenic. The spleen weighed 180 g. and measured 10 cm. × 5 cm. × 3 cm.

TABLE II

CLINICAL DETAILS OF SERIES

| Case No. | | Age (years) | Sex | Blood Pressure (mm.Hg) | Principal Disease(s) | Spleen Weight (g.) | Splenunculus | Congenital Anomalies | Size of Aneurysm (cms.) | Situation |
|---|---|---|---|---|---|---|---|---|---|---|
| C.R.H. | Series | | | | | | | | | |
| 977 | 1 | 50 | M | 140/90 | Carcinoma of stomach | 150 | 1 | — | 2·5 | At main bifurcation |
| 1002 | 2 | 74 | M | 160/90 | Tabes dorsalis | 180 | — | — | 1·0 | At second bifurcation |
| 872 | 3 | 90 | F | 180/80 | Carcinoma of stomach, myocardial infarction | 120 | — | — | 1·2 | At third bifurcation |
| 859 | 4 | 64 | F | 130/75 | Carcinoma of stomach | 140 | — | — | 0·8 | At main bifurcation |
| 0/449 | 5 | 69 | M | 170/70 | Serum positive "latent" lues, carcinoma of prostate, osteitis deformans, myocardial infarction | 225 | — | — | 0·8 | At main bifurcation |
| 1034 | 6 | 80 | F | 150/80 | Myelofibrosis, carcinoma of cervix | 600 | 1 | — | 1·5<br>0·5<br>0·5 | At main bifurcation, on trunk at second artery, on trunk at second artery |
| 1015 | 7 | 85 | F | 260/115 | Myxoedema, bronchopneumonia | 115 | — | Polycystic kidneys Aneurysm of Circle of Willis | 0·4 | On secondary trunk |
| 1137 | 8 | 66 | M | 250/140 | Essential hypertension, cerebral haemorrhage | 180 | — | — | 0·3 | At secondary bifurcation |
| 883 | 9 | 77 | M | 120/70 | Bronchopneumonia, bronchiectasis | 105 | — | — | 0·8 | At secondary bifurcation |
| 0/190 | 10 | 94 | F | 150/70 | Gangrene of leg due to femoral artery thrombosis | 160 | — | Cystic disease of pancreas, multiple renal cysts + jejunal diverticula | 0·8 | On main trunk |
| 1203 | 11 | 92 | F | 160/90 | Pulmonary embolism, thyrotoxic heart failure with atrial fibrillation | 210 | 1 | — | 0·7 | At secondary bifurcation |
| 1049 | 12 | 77 | F | 270/140 | Essential hypertension, gangrene of right leg due to popliteal artery thrombosis, multiple cerebral thrombosis | 240 | — | Osler's multiple hereditary telengiectasia | 1·5 | At secondary bifurcation |
| 986 | 13 | 82 | F | 200/110 | Myocardial infarction | 180 | — | — | 0·4 | At secondary bifurcation |
| 1550 | 14 | 80 | M | 115/80 | Bronchopneumonia, chronic pyelonephritis, benign prostatic hypertrophy | 200 | — | — | 1·0 | At main bifurcation |
| 1339 | 15 | 48 | F | 140/70 | Tuberculous bronchopneumonia miliary | 400 | — | — | 1·2 | At secondary bifurcation |
| 2138 | 16 | 92 | F | 200/100 | Bronchopneumonia, essential hypertension, cerebral thrombosis, cardiac infarction | 140 | — | — | 0·5 | On trunk of main vessel |
| 3414 | 17 | 74 | F | 130/60 | Diabetes mellitus, gangrene right leg, bronchopneumonia | 120 | — | — | 0·08 | At secondary bifurcation |
| 3431 | 18 | 74 | M | 240/120 | Chronic pyelonephritis with hypertension, cardiac infarction, cerebral thrombosis, bronchopneumonia | 180 | — | — | 1·2 | At secondary bifurcation |
| 2858 | 19 | 78 | F | 140/80 | Diffuse lupus erythematosus, carcinoma of breast, pulmonary embolism | 130 | — | — | 2·0 | At main bifurcation |
| 162 | 20 | 60 | F | 180/110 | Rheumatoid arthritis, acute-on-chronic pyelonephritis with hypertension and uraemia | 160 | 1 (2·5 cms.) | — | 1·4 | At first bifurcation |
| 0/453 | 21 | 86 | F | 240/110 | Carcinoma of breast, acute-on-chronic pyelonephritis with hypertension, bronchopneumonia | 140 | — | — | 0·6 | At secondary bifurcation |
| 1785 | 22 | 86 | F | 140/85 | Carcinoma of urinary bladder, massive pulmonary embolism, cerebral thrombosis | 120 | — | — | 0·5<br>0·7<br>1·2 | On main trunk at first bifurcation<br>At second bifurcation |
| 2789 | 23 | 80 | F | 230/120 | Essential hypertension, cerebral thrombosis, bronchopneumonia | 150 | — | — | 0·5 | On trunk of main vessel |
| 3526 | 24 | 72 | F | 180/100 | Cerebral thrombosis, diabetes mellitus, bronchopneumonia | 120 | — | — | 1·0 | At first bifurcation |
| 69 | 25 | 77 | M | 210/110 | Osteitis deformans, essential hypertension, cerebral thrombosis, bronchopneumonia | 160 | — | — | 0·5 | At first bifurcation |
| 3541 | 26 | 81 | F | 130/75 | Coronary thrombosis, chronic gastric ulcer | 120 | — | — | 0·4 | At secondary bifurcation |

A thin-walled aneurysm 4 mm. in diameter was present immediately proximal to the bifurcation of one of the primary branches of the splenic artery: no splenunculus was present (Fig. 5).

Data of the 26 cases are summarized in Table II. One case only (No. 15) was associated with septicaemia; none of the aneurysms was mycotic; only two cases (Nos. 5 and 2) gave a history or showed evidence of syphilitic infection but in neither did the aneurysm microscopically show evidence of a luetic aetiology; two cases (Nos. 6 and 15) were associated with significant enlargement of the spleen but neither had portal hypertension; four cases (Nos. 1, 6, 11, and 20) had splenunculi; and three cases (Nos. 7, 10, and 12) had congenital abnormalities of other systems. All the aneurysms were saccular and "true" as defined by Turnbull (1915), *i.e.*, "dilatations of the artery bounded by one or more of the coats of the artery".

## Incidence

Textbooks have until recently made little or no reference to aneurysm of the splenic artery. The recent increase in the number of cases reported in the literature, and the surgical treatment recommended have, however, called attention to its existence; so that although Illingworth and Dick (1956) do not mention it at all, Muir (1958) does make scant reference to it as "an occasional finding". The condition is referred to, albeit very briefly, by both Holland and Bourne (1959) and by Rob and Smith (1956) in their textbooks of gynaecology and surgery respectively.

The combined post-mortem series of Emmerich (1888), Bosdorff (1889), Schrotter (1898), Müller (1902), Garland (1921), Ophüls (1926), Guy (1939), Sperling (1940), and Seids and Hauser (1941) totals 38 cases of aneurysm of the splenic artery out of 100,241 necropsies, an incidence of 0·03%, ranging from 0·01% to 0·23% (Table III).

The present finding of aneurysm of the splenic artery in 10·4% of a consecutive series of routine necropsies may be thought to be due to a particular hospital selection or bias, for example in age group; but out of 825 necropsies performed by one of us in a precisely similar series in the same hospital before this series of specially studied cases, aneurysm of the splenic artery was recorded only twice. It is highly probable therefore that the difference between these figures for the incidence of aneurysm of the splenic artery depends entirely upon the care exercised in looking for it. As only two cases of aneurysm of the splenic artery were recorded among 825 necropsies, whereas 26 were found out of the next 250 when this feature was specifically looked for, and as both these series of necropsies were comparable in respect of age, sex, and diseases, the latter incidence must certainly be construed as true and the former false. The common practice of examining the organs after their removal from the body either by the pathologist or the post-mortem attendant strongly militates against the discovery of aneurysm of the splenic artery, and especially if they are not large or unusually conspicuous.

TABLE III
INCIDENCE OF ANEURYSM OF THE SPLENIC ARTERY IN NECROPSY SURVEYS

| Author | Place | Total Necropsies | No. of Splenic Artery Aneurysms |
|---|---|---|---|
| Emmerich (1888) | Munich | 8,669 | 1 (0·01%) |
| Bosdorff (1889) | Kiel | 3,108 | 7 (0·23%) |
| Von Schrotter (1898) | Vienna | 19,300 | 4 (0·02%) |
| Müller (1902) | Jena | 10,360 | 9 (0·087%) |
| Garland (1921) | Boston | 4,100 | 3 (0·073%) |
| Ophüls (1926) | Stanford | 3,000 | 1 (0·03%) |
| Guy (1939) | Chicago | 5,000 | 2 (0·04%) |
| Sperling (1940) | Minneapolis | 33,810 | 7 (0·02%) |
| Seids and Hauser (1941) | Cleveland | 12,894 | 4 (0·03%) |
| | Total | 100,241 | 38 (0·03%) |
| Springorum (1933) | — | 50 | 4 (8%) |
| Ferrari (1938) | — | 143 | 14 (9·8%) |
| Bedford and Lodge (1960) | — | 250 | 26 (10·4%) |

As previous reports have been of isolated cases or have been concerned with large unselected series of necropsy records it may reasonably be inferred that the previously estimated incidence is erroneous and that the apparent rarity of aneurysm of the splenic artery is spurious. The true incidence of aneurysm of the splenic artery—and certainly in old people dying in hospital—is 10·4%. Russell (personal communication) agrees that the condition is much more common than appears to be generally believed.

The series of necropsies reported by Springorum (1933) and Ferrari (1938), which have been given little or no attention in previous reviews, support the considerably higher incidence found by us. Springorum (1933) found four cases of aneurysm in 50 consecutive necropsies, and Ferrari (1938) found 14 out of 143, an incidence of 8% and 9·8% respectively.

An unknown but probably considerable number of aneurysms of the splenic artery found incidentally at necropsy have undoubtedly not been recorded in the literature. Further evidence in support of the commonness of the condition is afforded by the many radiologists who have seen a number of aneurysms in practice (*c.f.* Fig. 6) although no large radiological series has as yet been published. The inference is inescapable that had these cases been recorded in the literature, the reported incidence of the condition would be more in keeping with that found in the present series.

FIG. 6.—*Multiple calcified aneurysms of the splenic artery shown incidentally by radiography.*

### SEX INCIDENCE

The crude sex ratio of males to females in the cases discussed by Owens and Coffey (1953) was 1 : 2 (63 males to 127 females) and by Sherlock and Learmonth (1942) 1 : 1·78 (42 males to 75 females). In the present series the crude ratio of males to females was 8:18, and the corrected sex ratio for numbers admitted is 7·4% to 12·7% or 1 : 1·7 of males to female.

Although these previous series and our own are not strictly comparable in that the former cases were not derived from a consecutive series, and a corrected sex incidence ratio is therefore not available, the figures are surprisingly similar.

The incidence of the condition is undoubtedly higher in females than in males and this is not to be explained by the greater number of female admissions to hospital nor by the greater number of females coming to post-mortem examination (see Table I). Sherlock and Learmonth (1942) state that ". . . splenic aneurysm sometimes declares itself during pregnancy and this may partly account for the larger number of females . . ."

We are unable to explain the greater incidence of this condition in females than in males but any immediate effect of pregnancy is certainly not applicable in our series.

This incidence is particularly interesting as aneurysms at all other common sites are undoubtedly more frequent in males.

### AGE INCIDENCE

The average age where this was known of the 113 cases discussed by Sherlock and Learmonth (1942) was 48 years, the youngest being 14 and the oldest 84 years. The average age in the series reviewed by Owens and Coffey (1953) was exactly the same, their series including 58 women of child-bearing years and 31 who were pregnant. In the present series the average age of the patients with splenic artery aneurysm was 76·4 years, the youngest being 50 and the oldest 94.

The greater average age of patients with aneurysm of the splenic artery in the present series is due without a doubt to the age selection exercised in admitting patients to the Cowley Road Hospital. Table I shows that only 29 of the 250 patients investigated were under 60 years of age.

The incidence by decades is shown in Table I and Fig. 7, and is remarkably uniform from 40 to 99 years (extrapolating at the extremes). No relationship is apparent between incidence and age, and therefore, although the numbers of patients investigated under 60 years of age and over 90 are too few to warrant valid deductions being drawn, there is nothing to contradict the supposition that this condition may well occur with similar frequency in younger age groups and would be discovered at necropsy if especially looked for.

This proposition, however, cannot be tested and the effect of age on the incidence of aneurysm of the splenic artery properly assessed except by investigating a large consecutive series of cases comprising all age groups, with particular reference to the splenic artery. Until such information is available it would appear to be more acceptable that the incidence of aneurysm of the splenic artery is nearer the 10·4% of the present study than the 0·03% of previous reported series.

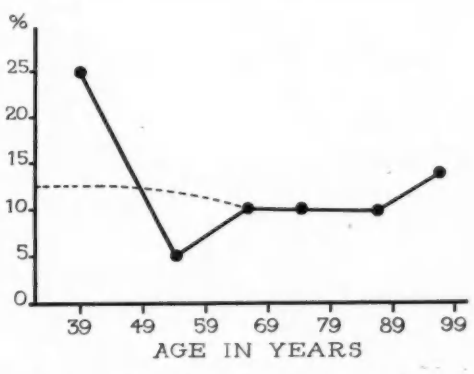


FIG. 7.—*Incidence of aneurysm of the splenic artery. (The dotted line is the mean of small numbers.)*

## Aetiology

Of the 125 cases described by Sherlock and Learmonth (1942), 74 were associated with some pathological condition which they considered to be a factor in the aetiology of the aneurysm.

As, however, aneurysm of the splenic artery may be expected to be found quite incidentally in 10·4% of all routine necropsies, previous views regarding its aetiology clearly demand reconsideration.

In the 204 previously reported cases (Owens and Coffey, 1953), a clearly defined aetiology has been proved in only comparatively few instances. In 36 cases the aneurysms were mycotic due to bacterial endocarditis; in two they were luetic; in 16 congenital; and four "false" aneurysms were traumatic. Sherlock and Learmonth (1942) consider that 34 out of the 125 cases they discussed were due to "arterial degeneration"; Owens and Coffey (1953) record 96 cases as "arteriosclerotic"; Turnbull (1915), however, more specifically stated that medial degeneration was the commonest cause of aneurysm of the splenic artery.

There appears to be an undoubted cause-and-effect relationship between rupture of aneurysm of the splenic artery and late pregnancy, a relationship reviewed in several papers and lately summarized by Chalmers (1949). Altogether 31 cases have been recorded of aneurysm of the splenic artery associated with pregnancy. But this association relates to a complication and not to the aetiology of the condition.

Many of the diseases which have been described as associated with aneurysm of the splenic artery were probably coincidental, *e.g.*, peptic and carcinomatous gastric ulcer, the Banti syndrome, malarial splenomegaly, "wandering spleen", thrombosis of the splenic artery, and Gaucher's disease. The two recorded cases (Owens and Coffey, 1953) of splenic arteriovenous aneurysm may well have been the result of rupture of a true aneurysm of the splenic artery into the splenic vein to which it had become adherent.

The apparent association with splenomegaly and portal hypertension may be fortuitous and not causal and may well have arisen from the greater attention that is directed to the splenic artery in these cases than is normally done in routine post-mortem examinations. Owens and Coffey (1953), however, record 32 such cases and believe that a rise in pressure in the portal system is an important aetiological factor.

In the present series of aneurysm of the splenic artery, none was mycotic; and although the Wassermann or Kahn reactions were positive in two patients, in neither case was syphilis considered to be the cause of the aneurysm. In all of our 26 cases, the aetiology was considered to be degeneration of the media, and although atheroma was present in the wall of all the aneurysms, it was held to be secondary to the medial degeneration. In three cases there were associated congenital abnormalities but these cannot be taken definitely to indicate that the splenic artery aneurysms were of the same (congenital) aetiology. The fact too that most of the aneurysms occurred at bifurcations of the splenic artery, *i.e.*, at the site where congenital defects in the media most commonly occur, although again suggestive, cannot be construed as convincing evidence of a congenital aetiology, for arterial bifurcations are also the site of election for medial degeneration. In this age group, atherosclerosis so often obscures the histological picture that it is rarely, if ever, possible to differentiate with certainty between congenital aneurysms and those due to medial degeneration.

Although of the 26 cases in the present series, 11 were hypertensive and all 26 had gross atherosclerosis of the splenic artery, neither hypertension nor atherosclerosis was considered to be the cause of the aneurysms. Turnbull (1915) comments on the association between aneurysms, medial degeneration, "excessive blood pressure", and gross atheroma, but stated that neither the raised blood pressure nor the atheroma caused the medial degeneration in his cases and hence were not aetiologically responsible for the aneurysm, *i.e.*, the fundamental aetiology of the aneurysm was medial degeneration and not hypertension or atherosclerosis; we concur with this view.

Thus, the only clearly defined and proved aetiological factors are (1) medial degeneration of the arterial wall, (2) mycotic due to bacterial endocarditis, (3) congenital defect in the vessel wall, (4) syphilis, and (5) trauma in the case of "false" aneurysms only.

Pregnancy appears to be a definite factor determining rupture of these aneurysms, and hypertension may also sometimes be responsible for this complication.

We are entirely in agreement with Turnbull (1915) that medial degeneration is by far the commonest cause of aneurysm of the splenic artery and this view is also shared by Russell (personal communication).

Further speculation on the aetiological role of other associated factors is profitless, for not only are such associations tenuous but also the fact that "incidental" aneurysms occur much more frequently than has hitherto been supposed makes the likelihood much greater that the aneurysm and the associated disease are only fortuitously related.

## Treatment

Of the 154 cases collected by Sherlock and Learmonth (1942), 56 (45%) were diagnosed as the result of rupture. This catastrophe has carried an overall mortality of more than 90%. Owens and Coffey (1953) record a mortality of 76% after rupture. Treatment by splenectomy before rupture, however, carried a much better prognosis, 18 out of 19 patients in Sherlock and Learmonth's series being cured and 29% in the Owens and Coffey series. It has therefore been inferred that operation should be undertaken as soon as the condition is diagnosed (Sherlock and Learmonth, 1942). This remains a reasonable inference in spite of the knowledge that splenic artery aneurysms are not only frequent but usually of no clinical importance, for if the diagnosis is suspected it will usually be as the result of some complication (unless discovered incidentally by radiology, see Fig. 6) and it is probable that in such cases rupture may be imminent, the well-recognized "two-stage" rupture. However, the fact that aneurysm of the splenic artery is apparently an innocuous condition occurring in over 10% of all elderly patients, and the considerable mortality among the (treated) cases assembled by Owens and Coffey (1953), provides a strong argument against routine surgery in patients without symptoms, a possible exception being made in pregnancy and in severe hypertension.

## Conclusions

In 250 consecutive routine post-mortem examinations made on patients dying in the Geriatric Unit, Cowley Road Hospital, Oxford, 26 cases were found to have aneurysms of the splenic artery, an incidence of 10·4%. None of the patients had symptoms referable to the aneurysm. This is a very much higher incidence than the total of 262 cases previously described in the world's literature suggests and than the stated incidence derived from the several large necropsy surveys. The condition occurs more commonly in females than in males. The literature of the condition is comprehensively reviewed.

Medial degeneration is considered to be the commonest aetiological factor.

The implications of the findings reported here are discussed.

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# A CASE OF SPONTANEOUS RUPTURE OF THE NORMAL LARGE BOWEL CAUSING HAEMOPERITONEUM

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A case of spontaneous partial rupture of the normal large bowel causing a haemoperitoneum is described. No similar case appears to have been reported previously.

Spontaneous rupture of the normal large bowel is a rare condition. In a recent article Cronin (1959) described two cases and reviewed a further 10 cases from the literature. In all 12 cases the rupture of the bowel was complete, with associated faecal soiling of the peritoneum. In the present case the rupture was partial, only the serous and muscular layers being involved.

## Case History

C.C., a man aged 59, a panel-beater, was admitted to hospital on September 1, 1959. While at work that morning he developed severe abdominal pain, at first colicky and generalized but later localized, persistent and sharp in the lower abdomen. Shortly after the onset he took a purgative which made the pain so severe that he fainted. He did not vomit but had no appetite and later felt persistently nauseated. He had had a normal bowel action earlier that day and had a further action after the dose of purgative.

Examination showed a man fit for his age, comfortable while lying still but with severe abdominal pain on movement. His temperature was 100·4°F., pulse rate 88/minute, respiration rate 20/minute, and blood pressure was 130/70 mm.Hg. There was marked foetor oris but the tongue was clean. No abnormality was found in the cardiovascular, respiratory, or central nervous systems. On abdominal examination there was marked guarding, tenderness and release tenderness over the right lower quadrant, and mild tenderness over the left hypochondrium. Liver dullness was present; bowel sounds were absent. No evidence of a hernia was found. Rectal examination showed some tenderness high up on the right. A diagnosis of acute appendicitis was made and the patient was operated on the same day, 18 hours after the onset of pain.

The abdomen was opened through a gridiron incision in the right iliac fossa. On opening the peritoneal cavity a large amount of blood was found and the appendix was normal. A right paramedian incision was then made and approximately 20 oz. of blood and clot removed from the peritoneal cavity. Most of the clot lay in the pelvis and was attached to the distal part of the sigmoid colon. When the clot was removed a longitudinal linear tear of the sero-muscular layers of the colon was revealed approximately 3 in. long; it affected the anterior taenia coli as it broadened out just above the rectosigmoid junction. Through this tear pouted colonic mucosa which appeared intact but was of a dark greyish colour. Apart from this tear no abnormality of the bowel wall was visible and there was no induration or inflammatory reaction. The edges of the torn sero-muscular layers were bleeding briskly. The cut edges of the tear were brought together with continuous fine chromic catgut and then oversewn. A transverse colostomy was fashioned and brought out through the upper end of the paramedian incision, which was closed with a drain to the pelvis.

Recovery was uneventful and later sigmoidoscopy and barium enema examination showed no abnormality of the bowel. Two months later the patient was re-admitted to hospital and the colostomy closed. Since that time he has remained well. Further enquiry after his first operation revealed that in infancy he had had a rectal prolapse and since that early age he had regularly taken large doses of purgative to ensure a daily bowel action. On first getting up he spent an hour on the w.c. each day, to ensure that defaecation was satisfactory. He denied the introduction of a foreign body or the self-administration of enemata.

## Comment

In the previously reported cases of spontaneous rupture of the large bowel, the bowel wall has been perforated. Various factors have been incriminated, for example, raised intraabdominal pressure due to straining or sudden stress, early diverticulosis with weakening of the muscular wall of the colon, stercoral ulceration due to impacted faeces, or the presence of an external hernia.

In four cases (Eadie, 1955; Hahn, 1931; Huntley, 1919; Weinstein and Roberts, 1952) the pain started while the patient was straining to defaecate. Of Henderson's (1957) two cases, one had had an enema shortly before laparotomy was carried out and the second had taken a purgative after the onset of abdominal pain. In one of the cases described by Cronin (1959), the precipitating factor was apparently a sudden rise in intraabdominal pressure due to a sneeze, but in the second no obvious cause could be found. This lack of obvious cause was also true of the two cases described by Brown (1944) and by Lataix (1949), although in the latter's case the presence of a large incisional hernia might have been a factor.

The probable cause of bowel rupture in the present patient was a rise in intraluminal pressure from overvigorous contraction of the muscle due to purgatives. It is not easy to dismiss as irrelevant his curious obsessive habits about his bowel movement. There was no weakness or thinning of the muscular wall of the bowel, which was of adequate thickness to be sutured safely and subsequent radiographs showed no evidence of diverticulosis. There was no stercoral ulcer, as the mucosa was intact, nor was an external hernia found at the time or subsequently.

I would like to thank Mr. C. G. Scorer, under whose care this patient was admitted, for his encouragement and permission to publish this case. I am also grateful to Mr. D. H. Patey and Mr. L. P. Le Quesne for their advice and help.

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# THE USE OF SOFRAMYCIN (FRAMYCETIN SULPHATE) FOR INTESTINAL STERILIZATION

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From its known properties "soframycin" appears to be valuable for intestinal antisepsis since it has a broad spectrum. The intestinal bacteria are sensitive to it, it acts rapidly, is poorly absorbed from the gastrointestinal tract, and is well tolerated by mouth.

"Soframycin" (framycetin sulphate) is prepared from *Streptomyces decaris*. Its antibacterial spectrum is wide and it exerts both a bacteriostatic and bactericidal action on a number of Gram-positive and Gram-negative organisms (Massénat-Deroche, 1954). Staphylococci resistant to other antibiotics are highly sensitive to "soframycin" (Lutz and Hofferer, 1955a) and enterococci are sensitive in fairly low concentrations. The streptococcus requires relatively high bacteriostatic concentrations, especially for *Streptococcus viridans*, and Gram-negative organisms, especially coliform organisms, *Proteus* and *Pseudomonas pyocyanea*, are very vulnerable to "soframycin" (Lutz and Hofferer, 1955b), and the bactericidal potency of "soframycin" against *Proteus* is greater than that of the other usual antibiotics. Pathogenic coliforms, especially the well-defined antigenic strains occurring in infantile gastroenteritis, are very sensitive to the antibiotic (Connell and Rousselot, 1958; Louwette and Lambrechts, 1958).

"Soframycin" is readily absorbed when given parenterally, but because of toxicity it is not given therapeutically by this route. By contrast "soframycin" is but poorly absorbed when given orally because the intestinal barrier is almost impermeable to it and thus the antibiotic can exert a sustained effect on the intestinal flora.

It is necessary to reach a single oral dose of 4 g. of "soframycin" before blood concentrations become measurable (about 1 $\mu$g. per ml.) (Massénat-Deroche, *loc. cit.*). In therapeutic doses absorption is so poor that there are no systemic effects, as estimations of blood "soframycin" levels have repeatedly shown. The urinary levels are too low to cause any renal damage (Marquézy, Debray, Leveau, Grenier, and Lepage, 1955).

## Clinical Trials

The clinical trial was conducted on 22 patients in the wards of Whittington or Hornsey Central Hospitals. All the patients to whom the drug was given were cases in which the bowel had to be divided for resection of a growth, for the establishment of a colostomy or ileostomy, or for the utilization of a portion of the bowel for another purpose, *e.g.*, ileal loop bladder or ureteroplasty. In all cases the patients were in hospital when the "soframycin" was administered. The drug was given in tablet form by mouth, 0·5 g. eight-hourly in the majority of cases, the total dosage varying from 2 g. to 4 g. The time and dose were recorded.

Patients were prepared for operation by the routine method used in the unit. No aperients were given but they had bowel washouts on the morning of the operation, on the evening preceding operation, and on the evening preceding that, *i.e.*, three in all. In the cases marked with a star in the Table, 250 mg. of "soframycin" in 60 ml. saline was instilled into the bowel after each washout and left to be passed by the patient as desired.

## Bacteriological Results

As far as possible, examination was made of (1) a specimen of stool passed recently before the first dose of "soframycin"; (2) a specimen passed after the last dose of "soframycin" and before operation; and (3) specimens of intestinal contents taken from the lumen of the portion of intestine removed at operation.

The specimens were examined on a quantitative basis, except in the case of small amounts of mucus or tissue, from the area of a malignant growth. The method was as follows:—

Weigh two equal portions of stool, approximately 1 g. Emulsify one portion in 100 ml. saline and dilute this emulsion 1 in 10, 1 in 100, and 1 in 1,000 in saline. Culture 0·1 ml. of each of these dilutions on desoxycholate citrate agar medium, on blood agar medium incubated aerobically, and on blood agar incubated anaerobically. After incubation, count the colonies on

## TABLE

### RESULTS WITH SOFRAMYCIN SUMMARIZED

| Initials | Sex | Age | Case No. | Condition for Operation | Dosage of "Soframycin" (g.) | Bacteria before "Soframycin" | Bacteria after "Soframycin" | Clinical Course |
|---|---|---|---|---|---|---|---|---|
| A.H. | ♂ | 69 | 1 | Resection of colostomy | 1·0, 8-hourly (total 4) | Not recorded | No coliforms, haemolytic strep., staph. or yeast per g. dried weight | Good |
| V.A. | ♀ | 56 | 2 | Hemicolectomy for carcinoma of caecum | 0·5, 8-hourly (total 2) | 1·8 million/g. dried wt. mostly coliforms | Very little growth, only 118/500 enterococci g. dried wt. | Good |
| L.E. | ♀ | 85 | 3 * | Anterior resection, carcinoma of recto-sigmoid | 0·5, 8-hourly, 1 instillation after each washout (total 2) | 2,000 million coliforms/g. dried wt. | Proximal to neoplasm, very few coliforms; distal to neoplasm, very few coliforms | Good |
| C.H. | ♀ | 54 | 4 | Partial colectomy, carcinoma of ascending colon | 0·5, 8-hourly (total 3) | Not recorded | Colon sterile, 12,000 coliforms/g. dried wt. in small intestine only | Good |
| E.P. | ♀ | 56 | 5 | Colectomy for ulcerative colitis; abdomino - perineal one-stage resection | 0·5, 8-hourly (total 3·5) | Not recorded | Stool after 24 hours' treatment 160,000 enterococci/g. dried wt., after 48 hours, tissue and faeces from rectum, tissue and faeces from ileum, swab from ileum, all showed no coliforms but small numbers of enterococci and yeasts | Good |
| L.A. | ♀ | 69 | 6 | Resection of sigmoid colon and resection of 10 in. small bowel for colonic fistula after perforated diverticulitis | 0·5, 8-hourly (total 3) | Not recorded | (1) Proximal end of colon, very few viable organisms; (2) distal end of colon, distal to colostomy, large numbers Gram + ve bacteria, chiefly enterococci; swab of ileum, no viable organism | Good |
| C.H. | ♀ | 52 | 7 | Resection of colostomy | 0·5, 8-hourly (total 2) | Large growth 75 million/g. dried wt. almost all *E. coli* | (1) Proximal to colostomy, 1 million coliforms mostly Proteus (2) Culture of tissue, no growth | Good |
| E.H. | ♀ | 42 | 8 | Pelvic clearance with colostomy and ileal loop bladder | 0·5, 8-hourly (total 2·5) | Not recorded | No coliforms, large number of Gram + ve bacteria, chiefly enterococci | Pelvic abscess |
| D.M. | ♀ | 67 | 9 | Resection of carcinoma of splenic flexure | 0·5, 8-hourly (total 3·5) | 230 million/g. dried wt. organisms of which at least 23 million *E. coli* | No growth or organisms on any media | Good |
| | | | | | 0·5, 8-hourly (total 3·5) | 58 million/g. dried wt. mixed bacteria including 25 million *E. coli* | 30 million enterococci, no *E. coli* | Good |
| E.D. | ♀ | 69 | 10 | Resection of carcinoma of recto-sigmoid | 0·5, 8-hourly (total 2) | 27 million organisms/g. dried wt. of which 19 million *E. coli* | (1) Proximal end of specimen, 0·75 million *E. coli*/g. dried wt.; (2) distal end 0·66 million *E. coli*/g. dried wt.; (3) culture of tissue, no growth | Good |
| C.M. | ♀ | 63 | 11 | Colostomy for colo-vaginal fistula | 0·5, 8-hourly (total 2) | 192 million organisms, mostly coliforms | 6,080 coliforms/g. dried wt. | Good |
| J.A. | ♀ | 71 | 12 | Abdomino - perineal resection for carcinoma of rectum | 1·0, 8-hourly (total 4) | Not recorded | No coliforms, 14½ million enterococci/g. dried wt. | Good |
| E.F. | ♂ | 63 | 13 | Total cystectomy with ileal loop bladder | 0·5, 8-hourly (total 2) | Not recorded | Not recorded | Good |
| W.U. | ♂ | 76 | 14 | (1) Uretero-colic anastomosis | 0·5, 8-hourly (total 2) | 127 million bacteria, mostly coliforms | 2·13 million bacteria, mostly coliform and few enterococci | Good |
| | | | | (2) Total cystectomy and uretero colic-anastomosis remaining ureter | 0·5, 8-hourly (total 2) | 400 million bacteria, mostly coliforms | 6·4 million bacteria, mostly coliform; 1 day later, 2·4 million | Good |
| N.G. | ♀ | 76 | 15 | Resection for carcinoma of colon | 0·5, 8-hourly (total 3) | 930,000 organisms, mostly coliforms/g. dried wt. | No bacterial growth | Good |
| J.K. | ♀ | 79 | 16 * | Resection for carcinoma of recto-sigmoid | 0·5, 8-hourly + 1 instillation after each washout (total 2) | 100 million bacteria, mostly enterococci, with a few coliforms and *Cl. Welchii*/g. dried wt. | No bacterial growth | Good |
| E.W. | ♀ | 63 | 17 | Ileal loop for ureteroplasty | 0·5, 8-hourly (total 3) | 62·4 million bacteria, mostly coliform and some enterococci | No bacterial growth | Good |
| R.B. | ♂ | 32 | 18 * | Ileal loop bladder and total cystectomy | 0·5, 8-hourly + 1 instillation after each washout (total 3) | Not recorded | Not recorded | Good |
| F.P. | ♂ | 67 | 19 | Resection for carcinoma of sigmoid obstructing the bowel | 1, 8-hourly (total 4) | 400 million/g. dried wt. mostly coliform and enterococci | Proximal end of specimen, 126,000 organisms/g. dried wt., mostly enterococci; distal end sigmoid obstruction, 12·2 million/g. dried wt. | Good |
| A.P. | ♂ | 54 | 20 | Resection of benign ulcer of transverse colon | 0·5, 8-hourly (total 2) | Not recorded | Not recorded | Good |
| A. | ♂ | 52 | 21 | Total cystectomy and ileal loop bladder | 0·5, 8-hourly (total 2) | Not recorded | Not recorded | Good |
| F.S. | ♂ | 71 | 22 | Carcinoma of sigmoid, colon resected | 0·5, 8-hourly (total 2) | Not recorded | Not recorded | Good |

all plates where growth was not confluent. Dry the second portion of specimen in a desiccator and weigh the dried specimen in order to calculate the number of colonies per gram of dried specimen. From the appearance of colonies and from films of the colonies and of the original specimen, determine the approximate distribution of different bacterial species. Filter sufficient of the first (1 in 10) dilution of the original emulsion (equalling 1 in 1,000 of faeces) and test for the presence of free antibiotic by the disc technique.

## Results

In all cases the drug caused a marked reduction in the intestinal bacterial content, particularly in the coliform group of organisms and of *Cl. welchii*. Comparatively, enterococci were more resistant but they were much reduced in almost all patients. In several instances (Cases 15, 16, and 17) there was no growth of organisms at all in the stool after total dosages of 2 or 3 g. "Soframycin" was not detected by the disc technique in the specimens tested.

In only one case in which "soframycin" was used was there subsequent sepsis or complication of any kind, namely, in Case 8, a patient who had vesicovaginal and vaginocolic fistulae after previous radiotherapy for advanced carcinoma of the cervix, with gross sepsis before operation. One patient died from a pulmonary embolus on the sixth day after operation, and one, uraemic before operation, died in uraemia on the tenth post-operative day.

## Side-effects

There were no side-effects attributable to the drug in any of the cases treated. In addition to the above-mentioned patients a number of others were prepared for resection of bowel but no resection was done at operation nor did they show any evidence of side-effects from the administration of the drug.

## Summary

"Soframycin" was given in total dosage of 2 to 4 g. to 22 patients before operations involving division of the large intestine (18 cases) or small intestine (four cases). The drug led to a very great reduction or to the complete absence of viable bacteria in the stools or at the site of surgical operation. Post-operative infection of the peritoneum or intestinal or surface wounds was absent in all patients except one whose tissues were severely infected before operation. Undesirable side-effects from the drug were not found.

We acknowledge with thanks the assistance of ward sisters and nurses who helped in the work involved and of Miss E. Hutchinson in the Group Laboratory. We are indebted to Dr. E. W. Tapley for discussion on this clinical trial, and to him and Roussel Laboratories Ltd. for a supply of "soframycin" tablets.

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# THE AUGMENTED HISTAMINE TEST WITH SPECIAL REFERENCE TO ACHLORHYDRIA

BY

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The Kay augmented histamine test has been used in a special study of 30 patients with pernicious anaemia and 136 other subjects suspected of having achlorhydria. The findings have been correlated with uropepsinogen excretion, serum levels of vitamin $B_{12}$, and gastric biopsy. The definition of achlorhydria is specially considered.

For many years gastric secretion was estimated by techniques in which test meals were given by mouth and serial samples of gastric aspirate were titrated for acid. The neutralization of the gastric acid by the substance of the test meal and the practical difficulty of titrating a turbid fluid containing food residues led to the search for other methods of gastric stimulation. Solutions of caffeine and alcohol, even pure water, were experimented with but eventually they were replaced by the injection of histamine, which proved to be the ideal stimulant of the secretion of hydrochloric acid. The dosage of histamine was, however, limited by its systemic effects to a total of 0·5 to 1·0 mg. histamine acid phosphate, which may be an inadequate stimulus, particularly in patients disturbed by the procedure of intubation.

In 1953, Kay developed the augmented histamine test in which the dose of histamine was preceded by a dose of an antihistamine drug which blocks the systemic effects of the histamine but does not reduce the effect on gastric secretion. By means of dose response curves, Kay showed that a dose of 0·04 mg. per kilogram of body weight or more of histamine acid phosphate had a maximal stimulatory effect on the secretion of gastric acid. This was supported by Marks (1956) who correlated the findings in the augmented histamine test with the parietal cell mass in excised human stomachs. There are a few exceptions, *e.g.*, antrectomy and vagotomy reduce the acid secretory response although the number of parietal cells remains unaffected (Kay, 1958), but in general the augmented histamine test may be regarded as providing a maximal stimulus to gastric secretion.

The objection of many people to intubation makes it difficult to establish the normal range of gastric secretion and the prevalence of achlorhydria. Published information is largely restricted to medical students and hospital patients. The largest series is that of Polland (1933). Using the single-dose histamine test, he found that the frequency of achlorhydria increased from zero below the age of 20 to approximately 30% at the age of 70.

However, we now know that figures such as these represent the frequency of hypochlorhydria and achlorhydria combined, rather than achlorhydria alone. Using the augmented histamine test, Card, Marks, and Sircus (1955) found no instance of complete achlorhydria in the first 500 subjects they examined except in those with pernicious anaemia. Later, Card and Sircus (1958) showed that 29 out of 58 subjects who had been achlorhydric to 0·5 mg. histamine base secreted acid after 2·0 mg. histamine base; of the 29 who secreted no acid, 23 suffered from pernicious anaemia.

We report here our own experience with the augmented histamine test, with special reference to patients showing apparent achlorhydria but not suffering from pernicious anaemia. The test was applied to patients in whom achlorhydria had been diagnosed by means of the gruel test meal, a small dose of histamine, or the diagnex test (Denborough, Retief, and Witts, 1958). The loss of acid secretion has been correlated with other tests of gastric function, such as excretion of uropepsinogen and secretion of intrinsic factor, and with the gastric histology.

## Material

The augmented histamine test was performed in 166 subjects.

Thirty had classical pernicious anaemia and were used as a standard of reference. Particular care was taken in

this group to exclude any other possible cause for megaloblastic anaemia, *e.g.*, steatorrhoea. The remaining 136 subjects were gathered from various sources.

Thirty-six were obtained through the records of the Department of Clinical Biochemistry. In these achlorhydria had been diagnosed as the result of a fractional test meal with gruel, or after 0·5 mg. of histamine subcutaneously, or with the two combined. Patients with pernicious anaemia were excluded from this group, as were subjects over 80 years of age or those suffering from gross disease.

In 71 patients achlorhydria had been diagnosed by the diagnex test; 32 of these suffered from iron-deficiency anaemia; the remaining 39 were patients with miscellaneous conditions who had been admitted to a general medical ward.

Twelve subjects were relatives of patients with pernicious anaemia who had been found in a previous survey to have achlorhydria either to the diagnex test or the ordinary histamine test (Callender and Denborough, 1957).

Seventeen subjects had had no preliminary screening test.

Excluding the patients with pernicious anaemia, the augmented histamine test was performed in 136 subjects and achlorhydria or extreme hypochlorhydria was found in 64. Eight of these 64 had had a partial gastrectomy and they will not be considered further here; 11 others were not studied further for various reasons. There thus remained 45 subjects who had achlorhydria or extreme hypochlorhydria in the augmented histamine test and who did not suffer from pernicious anaemia. The majority of these cooperated in further tests of gastric function.

## Methods

Augmented Histamine Test.—The augmented histamine test was performed as originally described by Kay (1953) with minor modifications. Bronchial asthma was considered a contraindication. Pulse and blood pressure readings were recorded during the test and special care was taken when the systolic pressure fell below 110 mm. Hg. A Ryle's tube was used for aspiration and was adjusted in position by radiographic screening until the tip lay over the vertebral column in the midline; then, with the patient lying on the left side, continuous aspiration was started by means of an electric pump. To ensure a steady flow, constant supervision was necessary and when the volumes of juice were small, as in pernicious anaemia, continuous suction by hand often proved essential. The patient was asked not to swallow saliva but to spit it out. After 15 minutes' aspiration an intramuscular injection of 100 mg. of mepyramine maleate ("anthisan") was given, followed half an hour later by a subcutaneous injection of 0·04 mg. per kg. body weight of histamine acid phosphate. The 45-minute prehistamine sample was pooled but the posthistamine juice was collected as three separate quarter-hourly specimens.

Pre- and posthistamine samples were analysed as follows:—

(*a*) Volume was recorded in millilitres, and bile, mucus and blood content empirically indicated as $-$, $\pm$, $+$, $++$.

(*b*) The *p*H was determined in a direct-reading *p*H meter; occasionally samples were too small for this and "universal" indicator paper had to be used.

(*c*) Specimens were titrated with N/20 NaOH in a comparator block against a phosphate buffer standard of *p*H 7·4; neutral red was used as indicator.

The most direct measure of gastric secretion is the volume of juice produced on maximal stimulation. This is difficult to measure accurately as the stomach is open at both ends, but there is a close correlation between the volume of juice which can be aspirated and the amount of acid in it. Titration is not accurate when there is achlorhydria or hypochlorhydria, and it is essential to measure the *p*H of the gastric juice. Achlorhydria is theoretically present when the *p*H of the gastric juice is the same as that of the non-parietal gastric secretion, which is mainly derived from the pyloric glands, but this *p*H is not exactly known. Various arbitrary figures have been used such as 7·4, which is the *p*H of blood, 7·0, which is the physico-chemical neutrality, and 6·0, which is the lowest level commonly found in pernicious anaemia.

It has long been a convention to define the presence or absence of acid secretion in terms of titration with Töpfer's reagent. Patients with gastric juice less acid than *p*H 3·5 have been regarded as having achlorhydria. For the purpose of the present work we have extended this definition and applied the term "achlorhydria" when the *p*H of the gastric juice is never less than 3·5 and does not change more than one unit to the acid side after maximal stimulation with histamine. The term "hypochlorhydria" is used when the gastric juice becomes acid by more than one *p*H unit after histamine but does not become more acid than *p*H 3·5.

Uropepsinogen Estimation.—The uropepsinogen was estimated on a 24-hour specimen of urine, collected under toluene, by the method of Anson (1938), as modified by Aitken, Spray, and Walters (1954). Aitken and her co-workers found a normal range of 60 to 250 units (mean 136 units) and for pernicious anaemia 0 to 55 units (mean 19 units). With the same method Retief (1959) found that 20 control subjects in the pernicious-anaemia age group excreted 8 to 266 units (mean 133·3 units) and 27 patients with pernicious anaemia 0 to 48 units (mean 19·4).

Estimation of Intrinsic Factor.—Secretion of intrinsic factor was assessed indirectly by measuring the proportion of an oral dose of 0·5 $\mu$g. $^{60}$Co-labelled vitamin $B_{12}$ which was unabsorbed and excreted in the faeces. In patients with pernicious anaemia who lack intrinsic factor 60 to 100% of the radioactivity is recovered in the faeces, whereas in controls only 14 to 46% is found (Badenoch, Callender, Evans, Spray, Richards, Turnbull, Wakisaka, and Witts, 1955; Retief, 1959). Patients who showed defective absorption were asked to repeat the test. With the second test 50 mg. of an active preparation of intrinsic factor (Lederle, IFC 45774-133) was given by mouth with the radioactive vitamin $B_{12}$.

SERUM VITAMIN $B_{12}$ ASSAY.—The level of serum vitamin $B_{12}$ was assayed microbiologically; *Lactobacillus leichmannii* was used as test organism (Spray, 1955). With this method control values range between 150 and 1,000 $\mu\mu$g. per ml.; in pernicious anaemia values are usually less than 100 $\mu\mu$g. per ml. (Spray and Witts, 1958).

GASTRIC BIOPSY.—Wood's flexible biopsy tube was used to take biopsies of the gastric mucosa under radiological control (Wood, Doig, Motteram, Weiden, and Moore, 1949). Specimens were divided into three groups according to the histological appearances (Badenoch, Evans, and Richards, 1957):—

Group I: Normal mucosa or superficial gastritis with no significant atrophy of gastric glands.

Group II: Atrophic gastritis with mild to moderate glandular atrophy.

Group III: Severe glandular atrophy of the degree associated with pernicious anaemia. These were subdivided into severe atrophic gastritis where there was evidence of considerable inflammatory change and gastric atrophy with minimal inflammatory cell infiltration and complete absence of parietal cells.

## RESULTS

GENERAL OBSERVATIONS ON THE AUGMENTED HISTAMINE TEST.—The volume of saliva produced during the test is usually small and unlikely to contaminate gastric aspirate significantly, except in occasional instances, when it should be obvious.

The gastric tube was first passed until it was thought to be in the stomach. The patient was then screened and the tube manipulated if necessary. In 28% of patients the tip of the tube was initially placed unsatisfactorily, either at the cardia or lower oesophagus, or in the duodenum. In another 16% the tip was in the fundus and therefore not satisfactorily situated for maximal aspiration (Retief, 1959).

Anthisan caused obvious drowsiness in 61% of cases; this came on approximately 15 minutes after the injection and lasted up to two hours. Two to three minutes after the histamine injection 95% of subjects noticed a feeling of warmth which lasted about 30 minutes; the skin flushed visibly for 40 to 60 minutes, and in 12% a generalized blotchy erythema appeared which did not irritate. True urticaria was not seen. Other side-effects included headache (7%), and lachrymation and nasal obstruction suggestive of hay fever (6%). Bronchospasm was not noticed. Histamine caused a slight rise in blood pressure in 12% of cases, but a transient fall in blood pressure, lasting approximately 30 to 45 minutes, was more common (61%). The drop in systolic pressure varied between 3 mm. and 65 mm. Hg (mean 19) and the diastolic between 3 mm. and 40 mm. Hg (mean 13). In one subject only was it considered wise to discontinue the test because of

TABLE I

THE AUGMENTED HISTAMINE TEST IN PERNICIOUS ANAEMIA SHOWING VOLUME AND *p*H OF ASPIRATE

| Subject | Prehistamine Aspirate | | Posthistamine Aspirate | | | | | | Total Vol. (ml.) | Maximum *p*H Change |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 15-Min. Specimen | | 30-Min. Specimen | | 45-Min. Specimen | | | |
| | Vol. (ml.) | *p*H (units) | Vol. (ml.) | *p*H (units) | Vol. (ml.) | *p*H (units) | Vol. (ml.) | *p*H (units) | | |
| P.T. | 13·0 | 6·71 | 7·8 | 7·72 | 2·5 | 8·36 | 3·6 | 8·12 | 13·9 | +1·65 |
| A.H. | 11·9 | 6·72 | 6·3 | 6·84 | 3·6 | 8·01 | 0·8 | — | 10·7 | +1·29 |
| W.B. | 26·0 | 6·99 | 9·5 | 6·80 | 5·0 | 8·10 | 5·0 | 8·04 | 19·5 | +1·11 |
| C.L. | 18·6 | 7·63 | 0·5 | 8·00 | 7·8 | 8·59 | 9·0 | 7·23 | 17·3 | +0·96 |
| J.Ha. | 5·8 | 7·08 | 0·5 | 7·50 | Trace | 8·00 | Trace | 8·00 | 0·5+ | +0·92 |
| L.McI. | 21·0 | 7·29 | 1·0 | 8·00 | 3·0 | 8·19 | 8·0 | 7·70 | 12·0 | +0·90 |
| B.V. | 3·6 | 8·06 | 3·4 | 8·86 | 2·3 | 8·70 | 1·9 | 8·00 | 7·6 | +0·80 |
| E.W. | 30·0 | 6·87 | 6·8 | 7·52 | 11·8 | 7·47 | 7·6 | 7·58 | 26·2 | +0·71 |
| L.P. | 15·6 | 7·25 | 8·9 | 7·56 | 5·7 | 7·54 | 6·5 | 7·94 | 21·1 | +0·69 |
| C.R. | 10·6 | 7·51 | 2·8 | 7·91 | 4·5 | 8·18 | 5·8 | 8·02 | 13·1 | +0·67 |
| R.W. | 19·0 | 7·10 | 4·5 | 7·46 | 2·5 | 7·65 | 2·6 | 7·76 | 9·6 | +0·66 |
| F.B. | 11·0 | 7·10 | 2·8 | 7·15 | 10·4 | 7·75 | 4·2 | 7·25 | 17·4 | +0·65 |
| M.G. | 21·0 | 7·33 | 3·8 | 7·94 | 7·2 | 8·06 | 1·4 | 8·00 | 12·4 | +0·63 |
| M.B. | 11·8 | 7·40 | 2·0 | 8·00 | 1·0 | 8·00 | 12·8 | 7·65 | 15·8 | +0·60 |
| H.F. | 28·0 | 7·46 | 0·0 | — | 0·0 | — | 1·8 | 8·06 | 1·8 | +0·60 |
| E.J. | 15·4 | 7·00 | 6·6 | 7·49 | 3·8 | 7·53 | 1·0 | 7·53 | 11·4 | +0·53 |
| J.H. | 8·0 | 7·50 | 1·5 | 8·00 | 0·0 | 8·00 | 0·5 | 8·00 | 2·0 | +0·50 |
| J.M. | 0·5 | 7·50 | 0·5 | 8·00 | Trace | 8·00 | 2·0 | 8·00 | 2·5+ | +0·50 |
| W.D. | 5·6 | 7·68 | 1·2 | 7·00 | 0·5 | 8·00 | 2·8 | 8·06 | 4·5 | +0·38 |
| A.W. | 27·8 | 7·89 | 2·8 | 7·82 | 4·4 | 7·71 | 4·6 | 8·26 | 11·8 | +0·35 |
| S.W. | — | 7·80 | — | 8·13 | — | 7·74 | — | 7·84 | — | +0·33 |
| T.S. | 14·2 | 7·59 | 8·0 | 7·54 | 9·6 | 7·84 | 4·8 | 7·71 | 22·4 | +0·25 |
| E.A. | 13·0 | 7·65 | 5·5 | 7·85 | 2·5 | 7·65 | Trace | 7·50 | 8·0+ | +0·20 |
| F.R. | 8·0 | 7·81 | 0·0 | — | 0·0 | — | 2·0 | 8·00 | 2·0 | +0·19 |
| D.J. | 12·0 | 8·02 | 8·0 | 7·98 | 1·5 | 8·10 | 8·8 | 8·17 | 18·3 | +0·15 |
| R.C. | 43·0 | 7·50 | 9·3 | 7·50 | 10·0 | 7·50 | 9·3 | 7·50 | 28·8 | 0 |
| M.S. | 4·3 | 8·00 | 0·7 | 8·00 | 2·2 | 8·00 | 1·0 | 8·00 | 3·9 | 0 |
| W.R. | 2·6 | 8·00 | Trace | 8·00 | Trace | 8·00 | 0·6 | 8·00 | 0·6+ | 0 |
| W.Y. | 4·0 | 7·50 | 0·5 | 7·50 | 0·6 | 7·50 | 2·0 | 7·26 | 3·1 | −0·24 |
| D.E. | 26·0 | 7·36 | 7·0 | 7·18 | 3·2 | 7·18 | 1·8 | 7·03 | 12·0 | −0·33 |
| Mean | 14·9 | 7·44 | 3·9 | 7·69 | 3·6 | 7·87 | 3·9 | 7·79 | 11·4 | +0·52 |

hypotension. The pulse rate increased in 70% of patients (mean 11 beats per minute; maximum 52 beats per minute); in 16% the rate slowed somewhat.

AUGMENTED HISTAMINE TEST IN PERNICIOUS ANAEMIA.—The disease classically associated with achlorhydria is pernicious anaemia. An augmented histamine test was done on 30 patients with this disease to obtain a standard of reference. The gastric aspirate showed various degrees of bile staining in 27 of the 30 subjects, with no significant difference between pre- and posthistamine samples. There was obvious mucus in the juice from all but two patients and traces of blood were evident in seven. The volume of aspirate was invariably small (Table I).

In four patients only did the total volume of juice after histamine exceed 20 ml.; three of these showed heavy bile staining suggestive of considerable duodenal regurgitation. There was no evidence of increased secretion after histamine stimulation. The mean total posthistamine volume (11·4 ml.) was in fact less than the mean prehistamine aspiration over the same period of time (14·3 ml.).

Electrometric measurements revealed a prehistamine juice more alkaline than *p*H 7·0 in all but four instances and the lowest reading was *p*H 6·71 (Table I). In two cases only did the *p*H change to the acid side after histamine and the shift was less than 0·33 units. In three there was no change in *p*H; in all the others the *p*H rose after histamine (Fig. 1). The mean maximum *p*H change indicated an increased alkalinity of 0·52 units.

ACHLORHYDRIA AND HYPOCHLORHYDRIA UNASSOCIATED WITH PERNICIOUS ANAEMIA.—In 45 subjects not suffering from pernicious anaemia, none of the samples was more acid than *p*H 3·5. These subjects were, therefore, by our definition, hypochlorhydric or achlorhydric. In 14 of these subjects the diagnosis was simple iron-deficiency anaemia, in four steatorrhoea, six were close relatives of patients with pernicious anaemia, four had rheumatoid arthritis, and 17 suffered from miscellaneous diseases, including gastric carcinoma, myxoedema, aplastic anaemia, and nutritional megaloblastic anaemia.

Visible bile was present in the juice of 38 patients. There was a tendency for bile staining to become more pronounced after histamine. Obvious mucus was present in variable amounts in the aspirate of all but one patient. There were traces of blood in 21 instances.

The volume of gastric juice obtained varied widely (Table II). The mean total posthistamine aspirate (19·5 ml.) was no larger than the prehistamine sample (20·5 ml.) collected over a similar period of time. Both these volumes are larger than those found in pernicious anaemia, but are considerably less than in normochlorhydric subjects (*vide infra*). There was no indication of an increased flow of secretion in response to histamine.

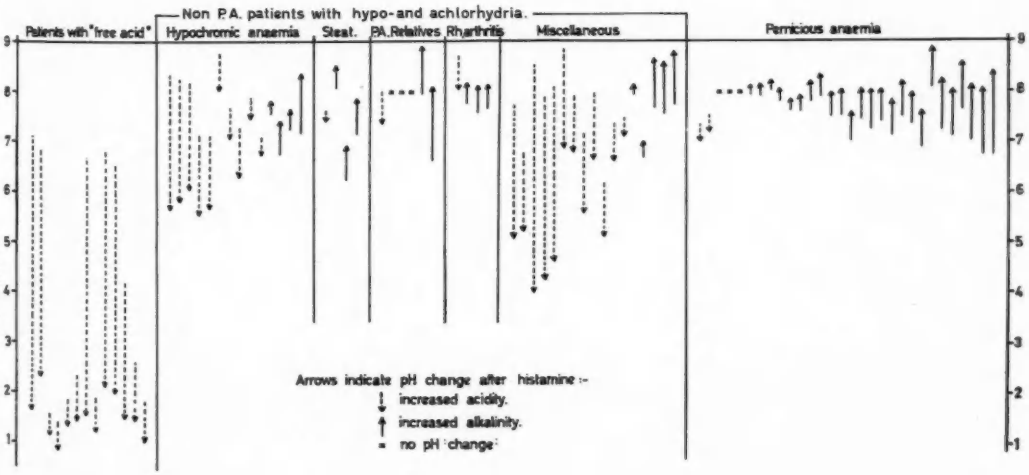


FIG. 1.—*Maximum changes in the* p*H of gastric juice in response to the augmented histamine test in patients with* (a) *free acid*, (b) *hypo- and achlorhydria, and* (c) *pernicious anaemia.*

TABLE II

AUGMENTED HISTAMINE TEST IN ACHLORHYDRIA AND HYPOCHLORHYDRIA UNASSOCIATED WITH PERNICIOUS ANAEMIA

| Subject | Prehistamine Aspirate (45 min.) | | Posthistamine Aspirate | | | | | | | Maximum *p*H Change (units) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 15-Min. Specimen | | 30-Min. Specimen | | 45-Min. Specimen | | Total Vol. (ml.) | |
| | Vol. (ml.) | *p*H (units) | Vol. (ml.) | *p*H (units) | Vol. (ml.) | *p*H (units) | Vol. (ml.) | *p*H (units) | | |
| H.Bo. | 56·0 | 5·22 | 16·0 | 6·13 | 13·0 | 6·04 | 12·0 | 6·62 | 41·0 | +1·40 |
| A.D. | 13·1 | 6·78 | 6·6 | 7·33 | 5·3 | 8·04 | 1·1 | 8·00 | 13·0 | +1·26 |
| C.D. | 11·4 | 7·15 | 2·7 | 8·21 | 6·8 | 8·05 | 2·0 | 8·00 | 11·5 | +1·06 |
| E.B. | 21·5 | 7·72 | 7·0 | 8·44 | 2·1 | 8·25 | 3·8 | 8·69 | 12·9 | +0·97 |
| E.L. | 69·0 | 7·54 | 3·4 | 8·12 | 2·0 | 8·84 | 14·0 | 7·56 | 19·4 | +0·94 |
| C.R. | 17·0 | 7·68 | 1·8 | 8·54 | 3·5 | 7·80 | 2·0 | 7·90 | 7·3 | +0·86 |
| F.H. | 5·1 | 7·94 | 2·8 | 8·75 | 2·4 | 8·22 | 4·0 | 8·68 | 9·2 | +0·81 |
| L.J. | 15·0 | 7·15 | 0·0 | — | 0·0 | — | 8·5 | 7·89 | 8·5 | +0·74 |
| A.Ha. | 18·0 | 6·25 | 20·8 | 6·35 | 10·6 | 6·55 | 10·5 | 6·90 | 41·9 | +0·65 |
| E.C. | 30·0 | 7·31 | 6·2 | 7·52 | 8·2 | 7·11 | 9·8 | 6·78 | 24·2 | +0·60 |
| R.S. | 14·5 | 7·65 | 2·0 | 8·06 | 5·9 | 8·07 | 12·0 | 7·78 | 19·9 | +0·42 |
| M.M. | 4·0 | 7·58 | 0·5 | 8·00 | 0·5 | 8·00 | Trace | 8·00 | 1·0+ | +0·42 |
| M.T. | 29·5 | 7·72 | 12·6 | 7·86 | 5·2 | 8·09 | 7·6 | 7·92 | 25·4 | +0·37 |
| R.T. | 14·6 | 8·09 | 5·0 | 8·42 | 7·8 | 8·23 | 13·8 | 8·13 | 26·4 | +0·33 |
| L.Lo. | 12·0 | 7·24 | 2·0 | 7·56 | 4·0 | 6·96 | 3·5 | 6·96 | 9·5 | +0·32 |
| L.U. | 23·4 | 6·69 | 11·6 | 7·00 | 23·2 | 6·77 | 19·5 | 6·61 | 54·3 | +0·31 |
| R.H. | 5·3 | 7·59 | 3·9 | 7·58 | 1·6 | 7·63 | 1·4 | 7·73 | 6·9 | +0·14 |
| W.H. | 58·0 | 7·95 | 11·5 | 8·00 | 6·2 | 8·06 | 11·8 | 8·08 | 29·5 | +0·13 |
| P.B. | Trace | 8·00 | 1·0 | 8·00 | Trace | 8·00 | Trace | 8·00 | 1·0+ | 0 |
| L.R. | Trace | 7·50 | Trace | 7·50 | 1·0 | 7·50 | 0·9 | 7·50 | 1·9+ | 0 |
| E.W. | 4·3 | 7·50 | 0·8 | 7·50 | 1·4 | 7·50 | 1·0 | 7·50 | 3·2 | 0 |
| G.F. | 21·8 | 7·54 | 10·3 | 7·48 | 9·8 | 7·57 | 8·0 | 7·59 | 28·1 | −0·06 |
| A.C. | 29·2 | 7·04 | 4·0 | 7·06 | 3·6 | 7·12 | 9·6 | 6·75 | 17·2 | −0·29 |
| J.F. | 4·8 | 7·47 | 2·0 | 7·50 | 4·2 | 7·12 | 4·6 | 7·06 | 10·8 | −0·41 |
| M.R. | 48·0 | 7·85 | 1·0 | 8·00 | 8·8 | 7·46 | 20·0 | 7·42 | 29·8 | −0·43 |
| A.H. | 42·3 | 7·24 | 20·7 | 7·52 | 26·2 | 6·80 | 16·3 | 7·10 | 63·2 | −0·44 |
| J.S. | 16·0 | 8·50 | 9·5 | 8·30 | 8·0 | 8·44 | 11·5 | 8·03 | 29·0 | −0·47 |
| L.L. | 24·2 | 7·68 | 5·2 | 7·42 | 3·2 | 7·21 | 4·0 | 7·11 | 12·4 | −0·57 |
| L.St. | 7·0 | 7·21 | 5·8 | 7·40 | 2·5 | 7·35 | 2·0 | 6·63 | 10·3 | −0·58 |
| T.W. | 1·0 | 8·00 | 3·2 | 7·51 | 4·6 | 7·38 | 4·0 | 7·80 | 11·8 | −0·64 |
| B.W. | 16·8 | 8·64 | 0·0 | — | 0·0 | — | 13·2 | 8·00 | 13·2 | −0·64 |
| M.D. | 32·0 | 6·18 | 21·5 | 5·16 | 26·8 | 5·70 | 8·5 | 7·10 | 56·8 | −1·02 |
| F.T. | 53·0 | 7·97 | 14·4 | 7·38 | 9·3 | 7·30 | 9·5 | 6·68 | 33·2 | −1·29 |
| E.P. | 2·0 | — | 3·0 | 6·58 | 1·0 | 6·60 | 7·0 | 5·16 | 11·0 | −1·42 |
| S.E. | 3·0 | 7·18 | 5·2 | 7·04 | 10·2 | 6·15 | 6·8 | 5·66 | 22·2 | −1·52 |
| M.H. | 4·0 | 6·61 | 1·2 | 7·00 | 2·4 | 5·20 | 2·0 | 5·06 | 5·6 | −1·55 |
| L.S. | 15·0 | 7·92 | 1·5 | 8·42 | 2·0 | 7·90 | 4·1 | 6·21 | 7·6 | −1·71 |
| A.S. | 35·0 | 7·16 | 5·1 | 5·51 | 3·0 | 5·14 | 6·1 | 5·24 | 14·2 | −2·02 |
| L.E. | 4·0 | 7·66 | 0·8 | 7·00 | 9·8 | 6·06 | 6·8 | 5·57 | 17·4 | −2·09 |
| W.T. | 16·0 | 8·64 | 1·0 | 7·77 | 4·5 | 7·67 | 2·5 | 6·33 | 8·0 | −2·31 |
| E.H. | 7·5 | 7·74 | 1·5 | 7·45 | 3·2 | 7·02 | 2·5 | 5·20 | 7·2 | −2·54 |
| J.R. | 18·8 | 7·60 | 0·0 | — | 11·5 | 5·13 | 9·0 | 4·69 | 20·5 | −2·91 |
| B.H. | 23·7 | 7·42 | 10·4 | 7·62 | 5·0 | 4·33 | 7·2 | 7·00 | 22·6 | −2·98 |
| H.B. | 28·2 | 8·10 | 15·3 | 8·48 | 6·7 | 7·54 | 8·5 | 4·09 | 30·5 | −4·01 |
| V.P. | 47·5 | 7·84 | 6·1 | 7·44 | 7·0 | 4·76 | 11·0 | 3·63 | 24.1 | −4·21 |
| Mean | 20·5 | 7·49 | 5·9 | 7·52 | 6·3 | 7·13 | 7·2 | 6·94 | 19·5 | −0·54 |

In 31 patients the *p*H showed a slight rise, no significant change, or fell by less than 1·0 unit after histamine. In these 31, therefore, the test indicated achlorhydria indistinguishable from that found in pernicious anaemia. In the remaining 14 subjects the gastric juice showed a *p*H fall of more than 1·0 with a maximum change of 4·21 units (Fig. 1); they showed, therefore, hypochlorhydria but not achlorhydria.

Titration of acid with NaOH was often technically difficult in view of the small volumes, the bile staining, and high mucus content of some specimens. There was no obvious correlation between *p*H values and titration figures (Fig. 2).

PERSONS WITH ADEQUATE ACID SECRETION.—The augmented histamine test was usually discontinued as soon as any sample more acid than *p*H 3·5 was obtained, but it was completed in 13 consecutive subjects in whom acid had been found in the gastric juice. The results are discussed briefly here for comparison with the findings in achlorhydria and hypochlorhydria.

Obvious bile staining was evident in the juice from four patients and much mucus in two. Traces of blood were found in seven tests.

Individual volumes varied greatly but the mean total posthistamine aspirate of 45 minutes (116 ml.) was much larger than the prehistamine collection (43 ml.; Table III). Both values greatly exceed those found in achlorhydria and hypochlorhydria. Quarter-hourly specimens showed maximal flow in the second and third posthistamine samples. Maximal acidity was invariably attained in the third

TABLE III

AUGMENTED HISTAMINE TEST IN PATIENTS WITH FREE ACID

| Subject | Age (years) | Diagnosis | Prehistamine Aspiration | | Posthistamine Aspiration | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | First Specimen | | Second Specimen | | Third Specimen | | pH Change (units) | Total Volume (ml.) |
| | | | Vol. (ml.) | pH (units) | Vol. (ml.) | pH (units) | Vol. (ml.) | pH (units) | Vol. (ml.) | pH (units) | | |
| K.B. | 79 | Hypochromic anaemia | 3·8 | 6·52 | 3·6 | 5·98 | 13·6 | 3·25 | 4·0 | 2·10 | −4·42 | 21·2 |
| B.S. | 70 | Gastric ulcer | 4·6 | 6·72 | 2·6 | 3·40 | 25·6 | 1·85 | 23·0 | 1·60 | −5·12 | 51·2 |
| H.P. | 60 | Hypochromic anaemia | 80·0 | 6·80 | 7·0 | 5·38 | 25·5 | 1·90 | 14·0 | 2·38 | −4·42 | 56·5 |
| R.P. | 60 | Pyelonephritis | 28·0 | 7·07 | 33·0 | 5·54 | 10·4 | 1·72 | 13·8 | 1·66 | −5·41 | 57·2 |
| L.P. | 73 | Hypochromic anaemia | 24·0 | 4·25 | 4·5 | 2·25 | 28·0 | 1·85 | 30·0 | 1·50 | −2·75 | 62·5 |
| F.R. | 26 | Normal | 33·0 | 1·60 | 14·6 | 1·46 | 13·5 | 1·32 | 44·0 | 1·28 | −0·32 | 72·1 |
| R.B. | 61 | Gastric ulcer | 43·8 | 6·83 | 26·5 | 4·85 | 32·0 | 2·61 | 18·0 | 2·31 | −4·51 | 76·5 |
| W.W. | 64 | Gastric ulcer | 43·0 | 2·60 | 21·0 | 1·75 | 35·0 | 1·65 | 27·5 | 1·45 | −1·15 | 83·5 |
| M.A. | 37 | Hypochromic anaemia | 43·6 | 2·36 | 31·0 | 1·65 | 33·0 | 1·46 | 34·0 | 1·40 | −0·94 | 98·0 |
| E.T. | 39 | Duodenal and gastric ulcer | 13·8 | 1·90 | 16·0 | 1·45 | 51·6 | 1·25 | 56·3 | 1·10 | −0·80 | 123·9 |
| M.S. | 26 | Normal | 91·5 | 1·75 | 49·0 | 1·35 | 65·0 | 1·32 | 71·0 | 1·22 | −0·53 | 185·0 |
| C.W. | 61 | Duodenal ulcer | 56·5 | 1·42 | 98·0 | 1·15 | 104·5 | 1·10 | 78·5 | 0·96 | −0·46 | 281·0 |
| A.P. | 42 | Duodenal ulcer | 93·0 | 1·80 | 94·0 | 1·35 | 150·5 | 1·16 | 95·0 | 1·16 | −0·64 | 339·5 |
| | Mean | | 43·0 | 3·97 | 30·8 | 2·89 | 45·2 | 1·73 | 39·2 | 1·55 | −2·42 | 116·0 |

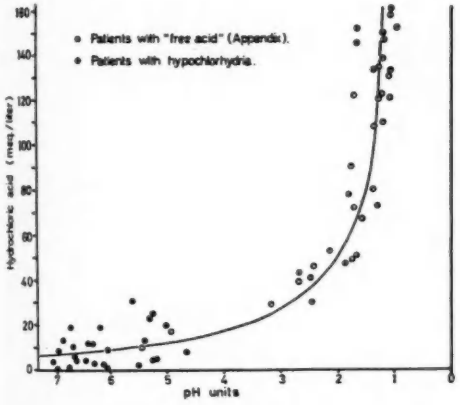


FIG. 2.—*The comparison of* pH *values for gastric juice and results of titration with N/20 NaOH to* pH *7·4.*

quarter-hour after histamine, where the mean *p*H was 1·55 (Table III).

In these patients with free acid there was a relation between acid titration values and *p*H (Fig. 2).

CORRELATION BETWEEN GASTRIC ACIDITY AND EXCRETION OF UROPEPSINOGEN, ABSORPTION OF VITAMIN $B_{12}$, SERUM VITAMIN $B_{12}$, AND GASTRIC HISTOLOGY.—Whenever possible the 45 subjects with achlorhydria and hypochlorhydria unassociated with pernicious anaemia were investigated further and the acid secretion was compared with other indices of gastric mucosal function. In Figs. 3 to 5 these patients are divided into three groups according to whether there was a *p*H fall greater than one unit (group 1); a fall in *p*H of less than one unit (group 2); or no change in *p*H after histamine (group 3). Control values and values for pernicious anaemia are included in each figure.

*Uropepsinogen Excretion.*—Forty-three of the subjects collected a 24-hour specimen of urine for uropepsinogen estimation (Fig. 3). In 31 the results were within the range for pernicious anaemia, low values being found in hypochlorhydria as well as in achlorhydria. The mean values in the achlorhydric subjects came into the range for pernicious anaemia and were lowest in those showing no change in *p*H. However, even in this group some values in the normal range were found.

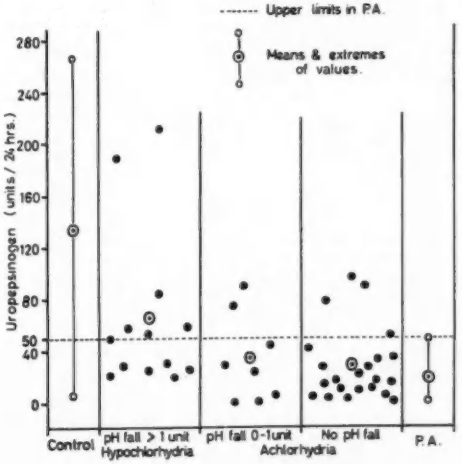


FIG. 3.—*Values for uropepsinogen excretion in patients with hypochlorhydria and achlorhydria compared with those in control subjects and patients with pernicious anaemia.*

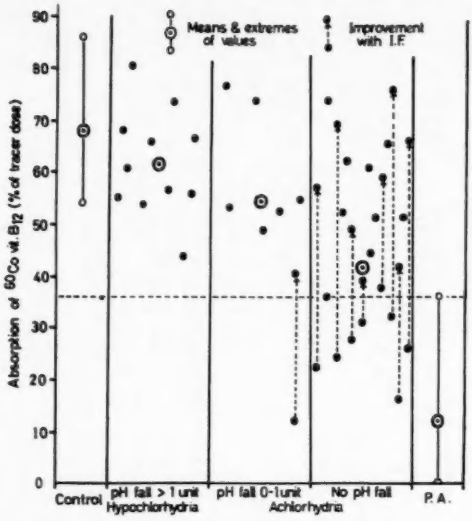


FIG. 4.—*Absorption from 0·5 μg. dose of [60] Co-labelled vitamin $B_{12}$ in patients with achlorhydria and hypochlorhydria compared with control subjects and patients with pernicious anaemia.*

*Absorption of [60]Co-vitamin $B_{12}$.*—Thirty-five subjects agreed to have a test of absorption of labelled vitamin $B_{12}$ (Fig. 4). In our laboratory, patients with pernicious anaemia have been found to absorb 0 to 36·3% of an 0·5-μg. oral dose of [60] Co-vitamin $B_{12}$ with a mean of 12%. The lowest absorption in a series of control subjects was 54%. Nine of the present subjects showed a reduced absorption, in the range for pernicious anaemia, although only in one was absorption reduced as low as the mean for pernicious anaemia. None of these patients was anaemic. They all fell into the truly achlorhydric group and only one showed any fall in *p*H after histamine. When the test was repeated with intrinsic factor absorption was enhanced.

A further 10 subjects showed absorption of vitamin $B_{12}$ intermediate between the range for normal people and pernicious anaemia. Eight of these were achlorhydric and two hypochlorhydric. In the remaining 16 absorption of vitamin $B_{12}$ was normal.

It would appear from these results that although several of the patients show evidence of lack of intrinsic factor, inasmuch as they fail to absorb labelled vitamin $B_{12}$ normally, the defect is in general not as severe as in pernicious anaemia. This, together with the fact that some of those with complete achlorhydria show normal absorption, supports the view that intrinsic factor is lost from the gastric secretion at a later date than acid secretion in the process of progressive mucosal atrophy (Witts, 1932; Poliner and Spiro, 1958).

*Serum Vitamin $B_{12}$* (Fig. 5).—Six patients were receiving vitamin $B_{12}$ therapy at the time of study.

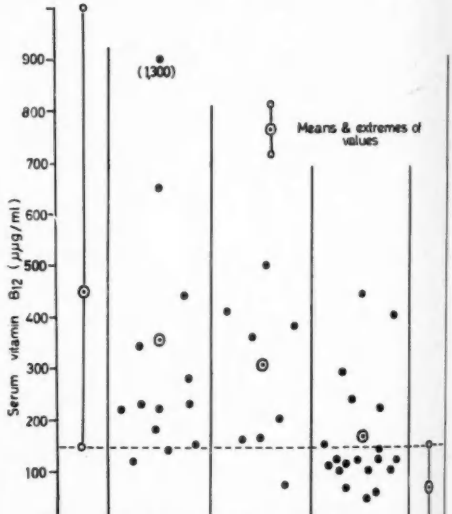


FIG. 5.—*Levels of serum vitamin $B_{12}$ in patients with achlorhydria and hypochlorhydria compared with values for control subjects and patients with untreated pernicious anaemia.*

TABLE IV

CORRELATION OF DIFFERENT ASPECTS OF GASTRIC FUNCTION IN HYPOCHLORHYDRIA AND ACHLORHYDRIA*

| | Hypochlorhydria % | Achlorhydria % | Low Uropepsin % | Low Absorption of Vitamin $B_{12}$ % | Low Serum Vitamin $B_{12}$ % |
|---|---|---|---|---|---|
| Hypochlorhydria | 100 | 0 | 54 | 0 | 18 |
| Achlorhydria | 0 | 100 | 80 | 38 | 54 |
| Low uropepsin | 23 | 77 | 100 | 38 | 41 |
| Low absorption of vitamin $B_{12}$ | 0 | 100 | 100 | 100 | 89 |
| Low serum vitamin $B_{12}$ | 12 | 88 | 75 | 53 | 100 |

*Low uropepsin < 50 u./24 hrs. Low absorption of [60]Co-$B_{12}$ < 40% tracer dose absorbed. Low serum vitamin $B_{12}$ < 150 μμg./ml.

The remaining 39 showed values for the serum vitamin $B_{12}$ ranging from 45$\mu\mu$g. per ml. to 1,300 $\mu\mu$g. per ml., with a mean of 265 $\mu\mu$g. per ml. The lowest values were found in patients with achlorhydria and no fall in *p*H after histamine. In 13 out of 19 in this group the serum $B_{12}$ was in the range for pernicious anaemia, though the mean was just above this. In three patients who had shown a significant increase in the acidity of the gastric juice after histamine, the serum vitamin $B_{12}$ level was also in the range for pernicious anaemia. There was, however, evidence of prolonged malnutrition in these three subjects and the low serum levels may have been due to dietary deficiency of vitamin $B_{12}$ rather than defective absorption.

*Histology of the Gastric Mucosa* (Fig. 6).—Suction biopsies were obtained in 28 of the 45 patients with achlorhydria or hypochlorhydria not suffering from pernicious anaemia. One further patient underwent a gastrectomy for carcinoma and the operation specimen was sectioned.

In order to correlate histology with function the three grades of mucosal degeneration have been compared with acidity changes, uropepsinogen excretion, vitamin $B_{12}$ absorption, and serum vitamin $B_{12}$ levels.

In this small series there was no linear relation between the degrees of atrophy on the one hand, and shift of *p*H after histamine, uropepsinogen values, or levels of serum vitamin $B_{12}$ on the other. However, there appeared to be a relation between loss of intrinsic factor and histology in that eight of the nine subjects who showed defective absorption of vitamin $B_{12}$ had advanced glandular atrophy. In the ninth there was moderate atrophy only. This relation was also evident in the serum levels of vitamin $B_{12}$ since 10 of the 12 who showed low levels of vitamin $B_{12}$ had severe gastric atrophy. The remaining two showed moderate atrophy only; one of these suffered from steatorrhoea.

Although gastric atrophy may represent the end-stage of atrophic gastritis, there is no close correspondence between the different degrees of loss of secretory ability and the different stages of gastritis as diagnosed by biopsy. The hypochlorhydric patient with the greatest increase in acidity had gastric atrophy on histological examination.

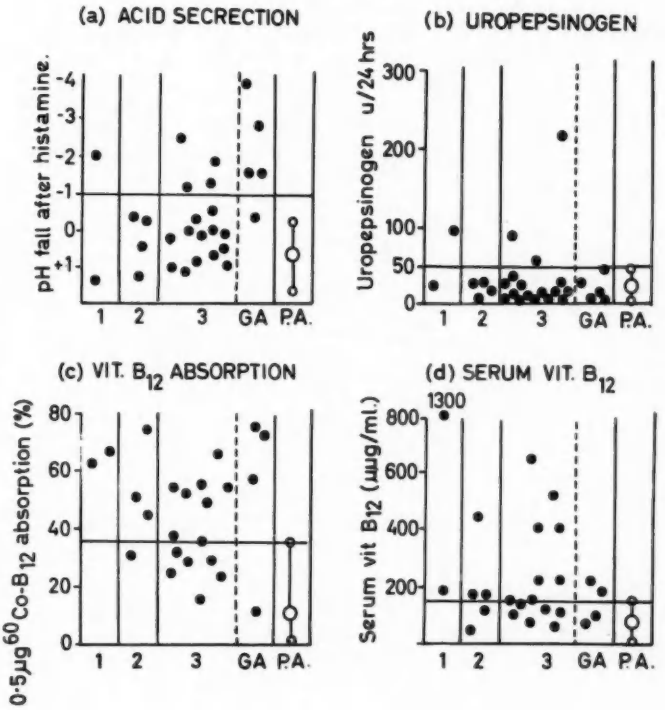


FIG. 6.—*Histology of the gastric mucosa compared with* (a) *acid secretion,* (b) *uropepsinogen excretion,* (c) *vitamin $B_{12}$ absorption, and* (d) *serum vitamin $B_{12}$. 1, No glandular atrophy; 2, moderate glandular atrophy; 3, severe glandular atrophy; GA, gastric atrophy.*

## Discussion

An augmented histamine test is something of an ordeal for a patient. The patient must fast, a tube must be passed, its position in the stomach must be checked by radiological examination, histamine and antihistaminic must be given in high dosage, and a skilled operator must supervise the whole procedure. Experience with the test has nevertheless shown that the diagnosis of achlorhydria by other methods is frequently erroneous. In any form of direct gastric analysis the position of the tube is of major importance and errors can easily be made. In indirect analysis, as in the diagnex test, the sources of error are more numerous but inadequate stimulation of the gastric mucosa may be the most important. It is probable that most of the surveys made to date exaggerate the prevalence of achlorhydria. Excluding patients with pernicious anaemia, about 60% of our patients diagnosed as having achlorhydria by simpler tests showed normal acid secretion in the augmented histamine test.

Electrometric titration of the *p*H of the gastric juice after maximal stimulation with histamine appears to be the most sensitive way of distinguishing between achlorhydria and hypochlorhydria. On the strength of our findings in pernicious anaemia we suggest that a fall in *p*H greater than one unit probably indicates secretion of acid by the gastric mucosa. Although we started by using the conventional *p*H 3·5 to separate those with normal acid secretion from those with hypo- and achlorhydria, our results indicate, like those of Card and Sircus (1958), that true achlorhydria is almost invariably associated with a *p*H greater than 6. The terms "free acid" and "total acid" based on titration with Topfer's and other indicators are meaningless and are best avoided. Simple tests *in vitro*, in which known quantities of HCl are added to alkaline gastric juice, show that the secretion of small amounts of acid will not be obvious unless careful measurements of *p*H are made (Retief, 1959).

*p*H readings are, however, of little value in assessing the quantity of acid secreted. Gastric juice is not a pure inorganic solution of acid but contains buffers which will influence direct calculations from the *p*H (Retief, 1959). Titration with NaOH to a specific neutral *p*H is then indicated. Unfortunately no satisfactory end-point exists as the acidity of non-parietal gastric secretion is not known. We have used *p*H 7·4 (the approximate *p*H of blood), but other workers have suggested *p*H 7·0, the physico-chemical neutrality point (Van Goidsenhoven, Wilkoff, and Kirsner, 1958) and 8·2, the *p*H of canine mucus (Shay, Komarov, Siplet, and Fels, 1946). We found a satisfactory correlation between *p*H and titration results in normochlorhydric individuals with gastric juice more acid than approximately *p*H 3·0 (Fig. 1). However, in hypochlorhydria titrations were technically difficult and results bore no constant relation to *p*H values. In these cases it might be physiologically more correct to titrate the prehistamine juice with HCl until the posthistamine *p*H is reached.

In only two patients with classical adult pernicious anaemia did the augmented histamine test reveal a maximal *p*H change towards the acid side after histamine stimulation; in neither instance did the *p*H fall by more than 1·0 unit. In 93% of cases the material aspirated became more alkaline. Few papers have been published relating experience with the augmented histamine test in pernicious anaemia, but Helmer, Fouts, and Zerfas (1932) and Kirsner, Nutter, and Palmer (1940) measured acidity changes after smaller doses of histamine and found no significant fall. Shay, Komarov, and Berk (1950) agreed that pernicious anaemia, as a rule, was not associated with increased gastric acidity after histamine, but reported one instance when the *p*H did fall from 8·71 to 6·42. Recently Jacobs (1958) reported a pronounced fall in *p*H in many of his cases of pernicious anaemia, even after fractional test meals with gruel and 0·5 mg. of histamine. His results are contrary to our findings and general experience. Abundant acid secretion is frequently found in the rare juvenile pernicious anaemia (Benjamin, 1948; Mollin, Baker, and Doniach, 1955; Stevenson, Little, and Langley, 1956; Harris-Jones, Swan, and Tudhope, 1957), but this condition is not identical with classical adult pernicious anaemia.

True achlorhydria with the augmented histamine test is not pathognomonic of pernicious anaemia. In our 31 patients with true achlorhydria but without pernicious anaemia the diagnoses included hypochromic anaemia, rheumatoid arthritis, steatorrhoea, aplastic anaemia, gastric carcinoma, and the healthy relatives of patients with pernicious anaemia. In such cases the uropepsinogen and absorption of vitamin $B_{12}$ are frequently reduced and in a substantial fraction they are in the range for pernicious anaemia (Fig. 3). The serum vitamin $B_{12}$ may also be reduced to the levels seen in pernicious anaemia.

The existence of cases in which the absorption of vitamin $B_{12}$ and the levels of vitamin $B_{12}$ in the serum are indistinguishable from those of pernicious anaemia, and yet the patient shows none of the symptoms of pernicious anaemia, no anaemia, glossitis, or subacute combined degeneration, has already been discussed in papers from this Department (Callender and Denborough, 1957; Witts, 1959, 1960). We regard them as examples of

latent pernicious anaemia. We know that they may remain latent for some years but we do not know the stimulus which causes the anaemia or other symptoms to become manifest. One of the chief applications of the augmented histamine test is in the recognition and study of cases of this kind.

There is no abrupt transition between achlorhydria and normochlorhydria, the gap being bridged by cases of hypochlorhydria in which, in our definition, the gastric juice never becomes more acid than *p*H 3·5 but there is a fall of more than one *p*H unit after maximal stimulation with histamine. Defective absorption of vitamin $B_{12}$, indicative of lack of intrinsic factor, was found only when maximal histamine stimulation failed to produce a significant fall in *p*H. Previous workers have noticed defective vitamin $B_{12}$ absorption in achlorhydria unassociated with pernicious anaemia, without differentiating between hypochlorhydria and true achlorhydria (MacLean, 1955; Schilling, Clatanoff, and Korst, 1955; Badenoch *et al.*, 1957).

Advanced gastric atrophy microscopically indistinguishable from that found in pernicious anaemia is known to occur in other conditions (Funder and Weiden, 1952; Joske, Finckh, and Wood, 1955; Coghill and Williams, 1958). On the other hand, Magnus (1958) found that only 40% of his patients with pernicious anaemia had true gastric atrophy; the rest showed extensive atrophic gastritis while 9% revealed fragments of surviving peptic and parietal cells. These observations imply that there is no pathognomonic anatomical lesion in pernicious anaemia. In the present series of patients not suffering from pernicious anaemia there was no constant relation between severity of atrophy and acid secretion, uropepsinogen, or serum vitamin $B_{12}$ levels, but intrinsic factor became defective only when glandular atrophy was advanced. There was no irrefragable evidence that histological gastric atrophy represents the end-stage of atrophic gastritis. It appears, however, that pernicious anaemia is associated with more complete secretory failure than other conditions where gastric biopsy may reveal atrophy of comparable severity. This might be explained on the basis of a diffuse total atrophy in pernicious anaemia as opposed to a patchy lesion in the other gastritides. It certainly stresses the point that the true state of the gastric mucosa is better assessed by functional investigation than single suction biopsies (Poliner and Spiro, 1958).

It has been suggested that progressive gastric atrophy results in the loss of acid, pepsin, and intrinsic factor in that order (Witts, 1932; Poliner and Spiro, 1958). The present study supports the view that intrinsic factor is lost at a later stage than HCl. Less than half of the achlorhydric patients showed evidence of absent intrinsic factor, while all of those with abnormal absorption of vitamin $B_{12}$ were truly achlorhydric, and had uropepsinogen values in the pernicious anaemia range. Nevertheless, this apparent sequence may be the result of a bias in our method of sampling. We began with patients with apparent achlorhydria. If sampling is done by first testing for intrinsic factor, then a fair proportion of cases will be found in which intrinsic factor is reduced before HCl is lost (McIntyre, Hahn, Conley, and Glass, 1959). Uropepsinogen bore much the same relation to vitamin $B_{12}$ absorption as did acid secretion, but as uropepsinogen bears no constant relation to gastric pepsin (Hirschowitz, 1957) these findings give no indication as to when pepsin secretion fails.

INDICATIONS FOR USE OF THE AUGMENTED HISTAMINE TEST.—According to present knowledge the augmented histamine test is the most efficient way of stimulating and assessing gastric acid secretion. In clinical research it should be used whenever attempts are made to find a correlation between disease states and the secretory capacity of the stomach.

In routine practice the test is probably of value in two groups of conditions only. In the differential diagnosis of megaloblastic anaemias it is often essential to differentiate achlorhydria from hypochlorhydria. Although conditions such as idiopathic steatorrhoea, megaloblastic anaemia of pregnancy, anaemia due to *Diphyllobothrium latum*, and megaloblastic anaemia associated with intestinal diverticulosis and blind loops may be associated with achlorhydria, any evidence of acid secretion is strong evidence against pernicious anaemia.

The other indication is in the study of hypersecretory states. Recent work has suggested that total acid output, in milliequivalents per hour, is a valuable figure in deciding the extent of operations for peptic ulcer (Bruce, Card, Marks, and Sircus, 1959). In duodenal ulcer the acid output usually exceeds 35 mEq. in the first hour after maximal histamine stimulation, while in gastric ulcer the acid output is significantly lower. The figure for normal adults varies between 10 and 35 mEq. per first hour. Stomal ulceration after operations for peptic ulcer is almost invariably associated with persistently high acid secretion.

## SUMMARY

The augmented histamine test was used to investigate the gastric secretion in 30 patients with pernicious anaemia and 136 other subjects suspected of having achlorhydria.

In pernicious anaemia the fasting juice is usually

more alkaline than *p*H 7·0. There is no increase in the volume of secretion after maximal stimulation with histamine and the juice usually becomes more alkaline. Rarely, the *p*H remains unchanged or there is a fractional shift towards the acid side, but always less than 1·0 unit.

We have diagnosed achlorhydria when the gastric juice is at no time more acid than *p*H 3·5 and when the fall in *p*H after maximal stimulation with histamine does not exceed 1·0 unit. If the *p*H is at no time below 3·5 but the fall after histamine exceeds 1·0 unit, we have diagnosed hypochlorhydria.

In approximately one half of the subjects found to have achlorhydria by less searching methods no specimen more acid than *p*H 3·5 was obtained after maximal stimulation with histamine. Of these, about two-thirds had complete achlorhydria and one-third hypochlorhydria.

In patients with impaired gastric secretion, not suffering from pernicious anaemia, there was some correlation between gastric acidity, uropepsinogen excretion and serum levels of vitamin $B_{12}$, the lowest mean values being obtained in those with complete achlorhydria.

Reduction of absorption of vitamin $B_{12}$ to the levels characteristic of pernicious anaemia was found only in patients with complete achlorhydria. In such cases the level of vitamin $B_{12}$ in the plasma may also be subnormal. We regard these patients as having latent pernicious anaemia.

The degree of gastric atrophy as determined by biopsy could not be correlated with change of *p*H after histamine, excretion of uropepsinogen, or serum levels of vitamin $B_{12}$, but defective absorption of labelled vitamin $B_{12}$ was found only in association with advanced gastric atrophy.

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# SOME FACTORS IN THE ASSESSMENT OF GASTRIC ANTISECRETORY DRUGS BY A SAMPLING TECHNIQUE*

BY

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Samples of gastric contents from patients with duodenal ulcer were more often highly acid when they drank 120 ml. of milk-cream mixture every hour than when they ate a bland diet. The volume of the drinks and the timing of the samples determined this apparent difference. Long-acting propantheline bromide reduced gastric acidity a little when the patients ate the diet and more when they took the drinks of milk-cream alone. It is concluded that the clinical usefulness of gastric antisecretory drugs can only be assessed under the actual conditions of use.

In 1958, Kasich and Argyros showed that a long-acting form of propantheline bromide, given in a dose of 120 mg. twice daily to patients with duodenal ulcer, often reduced the acidity of their gastric contents to *p*H 3 or 4 throughout the 24 hours. So as to control the variables of their experiment as closely as possible they gave their patients hourly drinks of a milk-cream mixture, during waking hours, without other food. When, in a pilot study, we repeated their observations but gave our patients a bland "gastric type" diet instead of the milk-cream drinks, we found that the drug produced no definite reduction in acidity. It seemed possible that our results differed from theirs because our patients took food.

This difference led to a study of the factors involved when gastric antisecretory drugs are assessed by a sampling technique. The following observations show that the acidity of any gastric sample depends on the interval since food was taken and on the amount and type of food. A comparison of the effect of propantheline† on a day when patients took hourly drinks of milkcream with that on a day when they took a standard bland diet confirmed that the effect of the drug was less when patients were taking the diet. Observations have also been made which indicate that propantheline affects the acidity of gastric samples more by reducing gastric secretion than by slowing the rate at which food leaves the stomach.

## METHOD

All patients studied had a typical, radiologically proven uncomplicated duodenal ulcer. They were encouraged to live as normal lives as possible in the ward. No drugs were given except for a hypnotic at night and propantheline. At the start of each experiment, a fine nasogastric tube was placed fluoroscopically so that the holes for aspiration lay over the vertebral column, in the likely position of the gastric antrum. At intervals of either 10 minutes or of one hour during the various experiments, 5-10 ml. samples of gastric contents were withdrawn. These were stored in a refrigerator until the *p*H of unfiltered specimens was measured with a sealed glass electrode. We calibrated the electrode between *p*H1 and 2, as well as at *p*H 4 and 9, since this was the range in which most of our observations were made.

In the main experiment to compare the effects of the drug when patients took two different diets, 12 patients were each studied for two periods of 48 hours. During one of these periods 120 mg. of long-acting propantheline was given by mouth every 12 hours. Each patient given this dose of propantheline was given smaller doses beforehand to find out whether this large dose could be tolerated. The conditions were changed on each of the four days as follows:

A: Hourly drinks of 120 ml. of a mixture of 3 parts milk and 1 part light cream taken on the hour from 8 a.m. to 9 p.m.

B: A standard bland diet (see appendix).

C: Hourly milk-cream drinks, propantheline at 8 a.m. and 8 p.m.

D: Standard diet, propantheline at 8 a.m. and 8 p.m.

* This paper was read at the annual meeting of the British Society of Gastroenterology in London on November 4, 1960.

† Pro-Banthine (prolonged action) kindly supplied by G. D. Searle and Co.

The order of these different conditions was varied from patient to patient in a latin-square pattern:

| | 1st Day | 2nd Day | 3rd Day | 4th Day |
|---|---|---|---|---|
| Patient 1 | A | B | C | D |
| Patient 2 | C | D | A | B |
| Patient 3 | B | A | D | C |
| Patient 4 | D | C | B | A |

This sequence was repeated three times during the investigation of the 12 patients; the double line separates the 48-hour periods. Observations began at 8 a.m. and continued until 7 a.m. the next morning. Samples were withdrawn every hour on the hour and immediately before doses of propantheline, drinks of milk-cream, or meals.

When the effect of giving different volumes of milk-cream or the mode of action of propantheline was studied in short experiments, observations were made in the morning, the patients having fasted since the previous evening. The tube was placed fluoroscopically as already described and, before observations were made, the stomach was emptied completely while the patient adopted different postures.

## RESULTS

The results of the 24-hour studies are shown in Figs. 1, 2, and 3. In each figure the results for all 12 patients are grouped together. Each section of the histograms in Figs. 1 and 3 compares the total number of samples in a particular *p*H range under two different conditions. Fig. 2 shows the mean acidity, calculated on an arithmetic scale, at each hour of the day during the test periods.

### The Effect of Food on the *p*H of Gastric Samples

Type of Food.—There were fewer very acid samples, below *p*H 2, and a greater number of samples, less acid than *p*H 2·5, when the patients took a diet than when they took the hourly drinks of milk-cream (Fig. 1a). These differences are statistically significant. The reason for this finding is seen in Fig. 2(a), which shows that the samples were consistently highly acid when the hourly drinks were taken, without the troughs of low acidity which occurred after meals. The differences at 9 a.m., 1 and 2 p.m., and 7 and 8 p.m. (one to two hours after main meals) are statistically significant ($P = <0{\cdot}05$).

Amount of Food.—This was most conveniently studied using a liquid food, in this case different volumes of milk-cream mixture. Fig. 4 shows that the acidity of the gastric contents fell after each drink, and fell to a lower level with a longer period of low acidity, as larger volumes were taken.

Buffering Power of Food.—Fig. 5 shows the buffering power *in vitro* of the milk-cream mixture against histamine-stimulated gastric juice compared

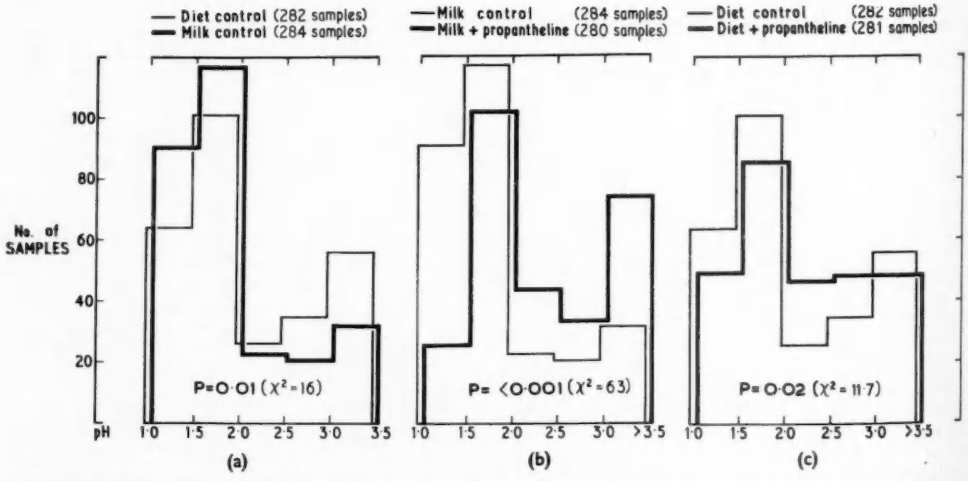


Fig. 1.—*The number of samples in different* p*H ranges under different conditions. Differences between the distribution of the samples have been assessed by the* $\chi^2$ *test* ($n = 4$). *Three of the results are shown. There is also a significant difference* ($\chi^2 = 16{\cdot}8$, $P = 0{\cdot}01$) *between the distributions when propantheline was taken with diet and when propantheline was taken with hourly drinks of milk-cream.*

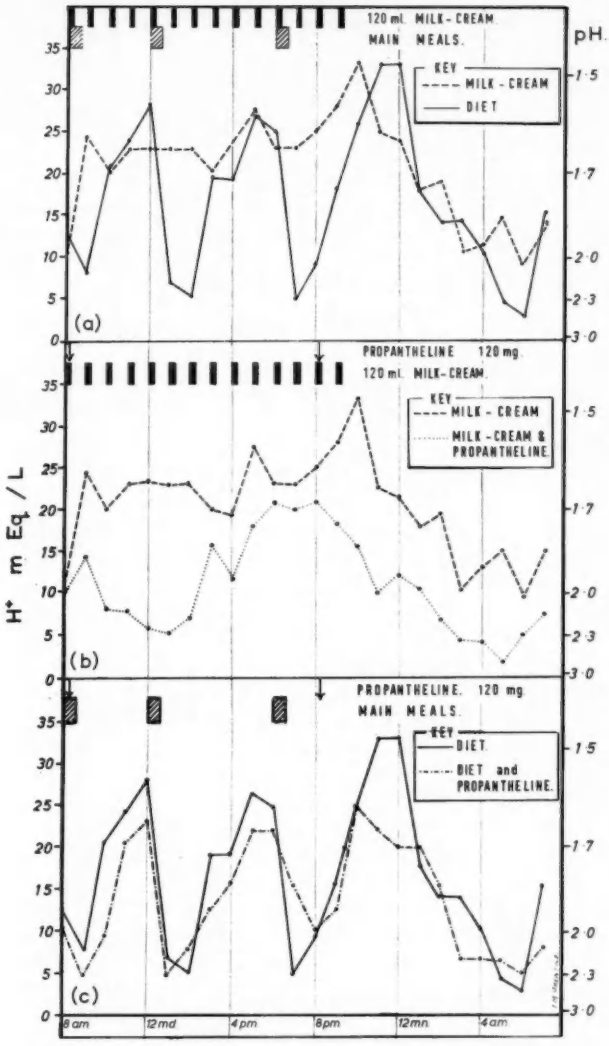


FIG. 2.—*The mean acidity at each hour of the day under different conditions.*

with the effect of simple dilution of the juice with water. The addition of milk-cream to a sample of gastric juice of equal volume reduced its acidity tenfold (*p*H 1 to *p*H 2). Skimmed milk and light cream each yielded almost identical curves.

TIMING OF SAMPLES AFTER FOOD.—Fig. 4 shows that the *p*H of samples withdrawn half an hour after a drink was different from the *p*H of samples withdrawn one hour after a drink. Before starting these experiments the stomach was completely emptied. Other experiments have shown that the fall in acidity is of shorter duration when the stomach is not emptied beforehand. Fig. 2(a) shows that the

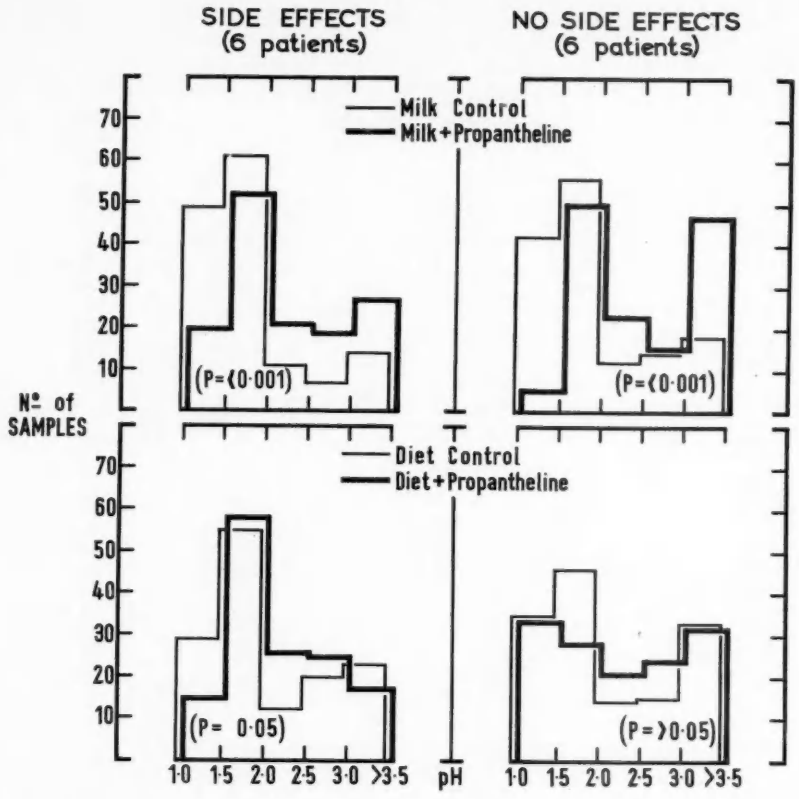


FIG. 3.—*The distribution of samples in different* p*H ranges among patients who experienced side-effects from propantheline compared with the distribution among those who experienced no side-effects.*

acidity of samples withdrawn after a meal depends on the length of time since the meal was taken.

### THE EFFECT OF LONG-ACTING PROPANTHELINE BROMIDE ON *p*H OF GASTRIC SAMPLES

WITH MILK-CREAM DRINKS.—After propantheline there were significantly fewer very acid samples below *p*H 2 and a greater number of samples which were less acid than *p*H 2·0 (Fig. 1(b)). This finding is illustrated in Fig. 2(b) which shows that the mean acidity of the samples was less after propantheline at every hour of the day. The differences between values from 9 a.m. to 2 p.m. (three to nine hours after the first dose of the drug) and 10 p.m. to 12 a.m. (four hours after the second dose) are statistically significant ($P = <0{\cdot}05$).

WITH DIET.—After the drug there were again significantly fewer very acid samples and a greater proportion of the less acid samples (Fig. 1(c)) than on the control day, but the differences were not so great as when milk-cream drinks were taken (Fig. 1(b)). The curves of mean acidity at each hour of the day (Fig. 2(c)) suggest that the peak acidities before meals and at night may have been reduced by propantheline, but the differences are not statistically significant.

A direct comparison between the two days when propantheline was given shows that there was a significantly ($P = 0{\cdot}01$) smaller proportion of samples more acid than *p*H 2 and a greater proportion of less acid samples when the milk-cream drinks were taken than when the diet was taken (Fig. 1(b) and (c)).

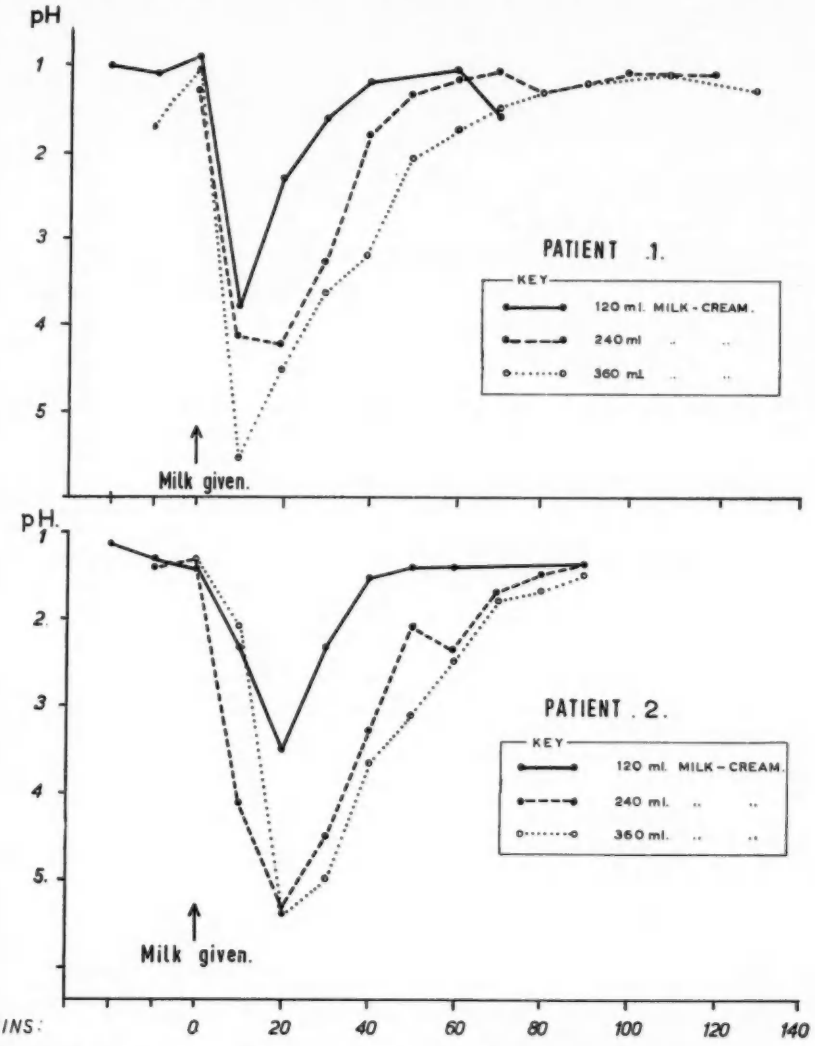


FIG. 4.—*The pH of gastric samples taken at 10-minute intervals after drinking different volumes of milk-cream.*

EFFECTIVE DOSE OF PROPANTHELINE.—During studies of the effect of drugs, including long-acting propantheline, on the secretion of acid under basal conditions, Sun, Shay, and Ciminera (1955) showed that to suppress secretion entirely the drugs had to be given in the maximal dose, "the optimal effective dose", that produced dryness of the mouth without other uncomfortable symptoms of parasympathetic inhibition.* Six of our patients experienced side-effects from the drug (Table I) and

* These authors found the "optimal effective dose" of long-acting propantheline bromide to be 30 mg., 60 mg., 180 mg., and 180 mg. in four patients. We chose 120 mg. as the standard dose so that our results should be comparable to those of Kasich and Argyros (1958).

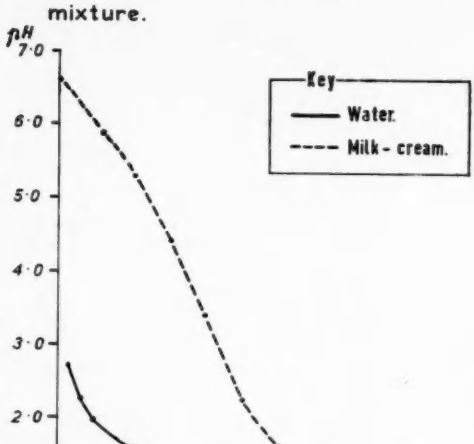


FIG. 5.—*The* p*H of histamine-stimulated gastric juice (125 mN) mixed in different proportions with water or milk-cream.*

TABLE I
SIDE-EFFECTS FROM LONG-ACTING PROPANTHELINE BROMIDE

| Patient | Side-effects from Propantheline | |
|---|---|---|
| | Day 1 | Day 2 |
| 3 | Dry mouth | Dry mouth, hesitancy of micturition |
| 6 | None | Slight hesitancy of micturition |
| 7 | Slight blurring of vision | Very dry mouth, hesitancy of micturition |
| 8 | None | Blurred vision, dry mouth, hesitancy of micturition |
| 10 | Dry mouth, blurred vision | Dry mouth, blurred vision |
| 12 | Dry mouth, blurred vision | Dry mouth, blurred vision |

six experienced none. The results in these two groups of six patients are shown in Fig. 3. On the day when milk-cream was taken, the effect of propantheline was apparently equal whether side-effects occurred or not. On the day of the diet, propantheline seems to have been effective only among those who experienced side-effects.

MODE OF ACTION OF PROPANTHELINE.—It has been shown that the *p*H of gastric samples depends on the interval since food was last taken and that propantheline, in a dose of 120 mg., reduces the number

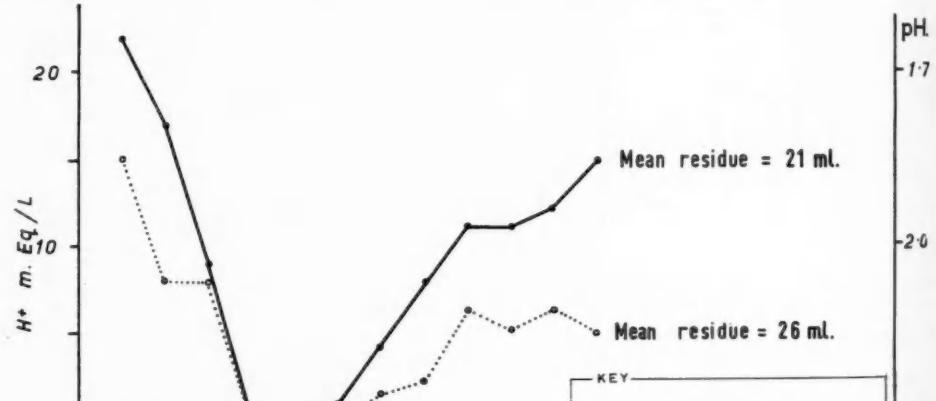


FIG. 6.—*The effect of a single dose of long-acting propantheline bromide, 120 mg., taken two hours previously, on the* p*H of gastric samples before and after a drink of milk-cream. The results shown are the mean of observations on six patients.*

of very acid samples found during a 24-hour observation period. It seems likely that such a drug could influence the *p*H of the samples in one or both of two ways. It could delay gastric emptying, so prolonging the buffering action of food, or it could reduce acid secretion. Using the sampling technique, some information about the relative importance of these two actions was obtained (Fig. 6). These curves show the mean acidity in six patients of samples taken at 10-minute intervals after a drink of milk-cream. The subjects were fasting and the stomach was emptied completely at the beginning and end of the experiment. The acidity of samples withdrawn before the drink was significantly ($P = <0{\cdot}05$) reduced by propantheline, 120 mg., given two hours previously showing that the drug had diminished acid secretion. At the end of the two periods there was no significant difference in the volume of the gastric residue. These findings are not conclusive but suggest that the drug reduced the acidity of samples 30-90 minutes after the drink more by reducing acid secretion than by slowing the rate at which milk left the stomach.

## DISCUSSION

Observations which show that there is a close correlation between the acidity in the stomach and the acidity of samples from the first part of the duodenum (Lopusniak and Berk, 1948; Atkinson and Henley, 1955) indicate the relevance of studies of gastric acidity in patients with duodenal ulcer. The technique of gastric sampling (James and Pickering, 1949) lends itself to a study of any effect which different diets or gastric antisecretory drugs may have on the acidity of gastric contents. Using this technique, several authors have shown that gastric acidity falls after a meal and rises to a maximum before the next meal (Nicol, 1939; Lopusniak and Berk, 1948; Watkinson, 1951). There are several good reasons why many authors who have studied the action of drugs by this technique have used a liquid food (Sun and Shay, 1956; Kasich and Fein, 1958; Kasich and Argyros, 1958; Thomson, 1958). The time of administration, the volume, and the buffering power of a drink can all be accurately determined. The observations in the present study have shown that it is essential to control these particular variables but they have also shown that there is a serious disadvantage in using a liquid food, as the results obtained may give a misleading impression of a drug's effectiveness under more normal conditions. Our results thus provide further evidence in support of the conclusion of Rowlands, Wolff, and Atkinson (1952) that drugs "must be tested under the actual conditions in which they are to be used. . . ."

Remarkably few studies have been made on the action of gastric antisecretory drugs under the conditions in which they might ordinarily be used (Atkinson, 1954; Nicol, 1939; Rowlands *et al.*, 1952). Atkinson demonstrated that a single injection of "banthine" reduced gastric secretion in patients with duodenal ulcer who were fasting; in half of them the aspirate became less acid than *p*H 3·5 after the drug. Yet when he gave the same drug orally, in the "optimal effective dose", four times daily and combined with large doses of alkali, to patients with duodenal ulcer taking a gastric-type diet, there was no definite reduction of acidity of the gastric contents during the day and a moderate reduction in only three out of five patients at night. In the present study it has been shown that long-acting propantheline bromide, given in large doses, slightly reduced the acidity of gastric samples from patients with duodenal ulcer who were taking a bland diet. Whether this reduction was enough to be clinically significant we cannot say, and we can do no more than speculate why the drug was apparently more effective with milk-cream drinks than with diet.

## SUMMARY

The length of time during which food lowers the acidity of the gastric contents is influenced by the quantity and nature of the food. It is therefore necessary to control the diet and the timing of samples when a gastric antisecretory drug is tested by a sampling technique.

The effect of giving a long-acting form of propantheline bromide to patients with duodenal ulcer on a day when they were taking hourly drinks of a milk-cream mixture has been compared with the effect obtained when they were taking a bland diet. There was a greater reduction in acidity with milk-cream drinks than with food. It is clear that unless gastric antisecretory drugs are studied under the ordinary conditions of use the results obtained are of doubtful clinical relevance.

We wish to thank Dr. K. E. Harris, Dr. J. C. Hawkesley, Dr. E. E. Pochin, Prof. M. L. Rosenheim, Dr. J. F. Stokes, Dr. D. Taverner, and Prof. R. E. Tunbridge for allowing us to study patients admitted under their care. Dr. E. N. Rowlands introduced us to the sampling technique and we thank him for much advice and help. The staff of the Dietetic Department, University College Hospital, under Miss C. F. Harris, made this study possible by their willing cooperation. We thank Mr. V. K. Asta and Mrs. Prentice for preparing the figures.

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## APPENDIX

### Standard Diet Used During this Study

| | |
|---|---|
| 6.0 a.m. | Weak, milky tea |
| 8.0 a.m. | Weak, milky tea |
| | Cornflakes with milk and sugar |
| | 1 egg, lightly boiled |
| | 3 slices thin bread and butter |
| | Jelly marmalade |
| 10.0 a.m. | Milk 5 oz. |
| 12.0 noon | 2 oz. tender mutton |
| | A medium helping of potato, mashed (2 oz.) |
| | A medium helping of sieved carrots (4 oz.) |
| | Pudding: ½ oz. cereal, 7 oz. milk, sugar, 1 tablespoon blackcurrant purée |
| 2.0 p.m. | Weak, milky tea |
| 4.0 p.m. | Weak, milky tea |
| | 3 slices of thin bread and butter |
| | Jam |
| 6.0 p.m. | Cream of vegetable soup |
| | 2 oz. cold breast of chicken |
| | 4 oz. mashed potato |
| | 1 "pola maid" ice cream |
| 8.0 p.m. | Milk 5 oz. |

*Gut*, 1960, **1**, 345.

# THE EFFECT OF AN ADRENAL INHIBITOR (SU 4885) ON GASTRIC SECRETION IN DOGS

BY

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There is considerable evidence that the adrenocortical steroids potentiate both human and canine gastric secretion. In this study, the action of the adrenocortical inhibitor, SU 4885, has been observed in dogs having separated pouches of the stomach. No effect was noted on the secretory responses to meat, histamine, or mecothane when the drug was given by single intravenous injection. However, the 24-hour output of acid was inhibited when the drug was given orally for a period of 10 to 14 days. While this effect may be due to the ability of the drug to inhibit adrenocortical function, there is no positive supporting evidence.

The recently synthesized compound 2-methyl-l-2-bis- (3-pyridyl)—l-propanone (SU 4885, Ciba) has been found to inhibit strongly adrenocortical function in the dog and in man (Chart, Sheppard, Allen, Bencze, and Gaunt, 1958; Jenkins, Meakin, Nelson, and Thorn, 1958; Coppage, Island, Smith, and Liddle, 1959; Jenkins, 1959). Studies *in vitro* have confirmed that it acts specifically on 11-$\beta$hydroxylation (Liddle, Island, Lance, and Harris, 1958), inhibition of which depresses the secretion of cortisol, corticosterone, and aldosterone by the cells of the adrenal cortex. The minimum effective dose of SU 4885 bitartrate is 5 mg. per kg. body weight and it has been shown that 15 mg. per kg. body weight administered intravenously promptly reduces the output of cortisol in the adrenal vein blood (Liddle *et al.*, 1958).

There is considerable evidence that the adrenocortical steroids potentiate gastric secretion in dogs and man and the following studies were undertaken to determine if the administration of SU 4885 had an effect on the secretion of acid and pepsin by the stomach.

## METHODS

Tests of the effect of SU 4885 on gastric secretion were carried out in seven dogs with separated pouches of the stomach of Heidenhain type. In three dogs the effect of a single injection of SU 4885 on three types of secretory response was studied, and in the remaining four dogs the drug was administered daily for a period of 10 days while the 24-hour secretions from the pouches were being collected serially.

SINGLE INJECTION OF SU 4885.—In three dogs the effect of an intravenous injection of SU 4885 bitartrate (15 mg. per kg. body weight) on the secretory response from separated pouches to meat, to a parasympathomimetic drug, and to histamine was determined. The dogs were kept under identical living conditions and fed on standard kennel rations; tests were carried out after a 16-hour fast and only when there was no free acid in the basal juice.

*Meal of Meat.*—After the ingestion of $\frac{1}{2}$ lb. of proprietary tinned meat, juice was collected at 15-minute intervals for four hours. In three tests on each dog an intravenous injection of SU 4885 bitartrate in 0·9% saline (15 mg. per kg. body weight) was given 15 minutes after the meat had been eaten while in three further control tests a similar volume of 0·9% saline alone was given.

*Mecothane.*—In these tests pouch secretion was stimulated by the continuous subcutaneous infusion of 5 mg. "mecothane" (carbaminoyl-$\beta$-methyl choline chloride) per hour at a constant rate using a Palmer injection apparatus. The injection was continued for four hours during which juice was collected from the pouch at 15-minute intervals. In three tests on each dog SU 4885 bitartrate in saline (15 mg. per kg. body weight) was injected intravenously immediately the infusion was started and in three control tests saline alone was injected.

*Histamine.*—The secretion of juice from the pouch was stimulated by a continuous subcutaneous infusion of histamine acid phosphate, 25 $\mu$g. base per kg. body weight per hour, delivered by a Palmer injection apparatus. When a steady rate of acid secretion had been reached, usually after one and a half to two hours, the juice from the pouch was collected for six 15-minute periods. An intravenous injection of SU 4885 bitartrate, 15 mg. per kg. body weight, was then given and collections continued for nine 15-minute periods. Cortisol hemisuccinate, 100 mg., was then injected intravenously and final six 15-minute collections made. Tests were

carried out on three occasions in each dog while in three further control experiments 0·9% saline was injected in place of the SU 4885 and cortisol was omitted.

In all the tests juice was collected at 15-minute intervals, the volume measured in millilitres and the concentration of free acid determined by titration with N/10 sodium hydroxide using Topfer's solution (*p*-dimethyl amino-azo benzene) as indicator. The concentration of pepsin in a 1 in 20 dilution of juice in distilled water was estimated by Hunt's method (1948) using dried human plasma as substrate and determining the amino-acid products of digestion by the Folin-Ciolteau reaction. The results were calibrated in milligrams tyrosine equivalents per millilitre juice. From these estimations the outputs of acid in milliequivalents and of pepsin in milligrams tyrosine equivalents per 15-minute periods were calculated.

In the responses to meat and "mecothane", statistical comparisons of the total outputs of juice, acid, and pepsin for the four hours of the test were made by an analysis of variance of the logarithms of the outputs.

CONTINUOUS ORAL ADMINISTRATION OF SU 4885.—In three dogs with separated gastric pouches of Heidenhain type, 24-hour collections of gastric juice were made by attaching a polythene bottle to the cannula draining the pouch. The dogs were fed a standard weighed diet of meat and cereal of equal amount each day. After a control period of two to three weeks, crushed tablets of SU 4885 were given each morning in milk for 10 to 14 days. The dose of SU 4885 was 100 mg. per kg. body weight per day. Daily collections of juice were made for a further 10 to 14 days after discontinuing the drug.

The volume of each 24-hour collection of juice was measured in millilitres and the concentrations and outputs of acid and pepsin were estimated as above. From these volumes the daily outputs of acid and pepsin were calculated.

The means of the logarithms of the outputs of juice and pepsin in each phase of the experiment for each dog were analysed statistically by Student's t test.

## RESULTS

SINGLE INTRAVENOUS INJECTION SU 4885.—The results are for three dogs.

*Response to Meat.*—The intravenous injection of 15 mg. SU 4885 per kg. body weight was without significant effect on the volume of juice or the outputs of acid or pepsin from the separated pouches in response to ingestion of a meal of meat. The mean outputs of acid and pepsin for each dog are shown in Fig. 1 and the mean total outputs during the four hours of the tests in Table I.

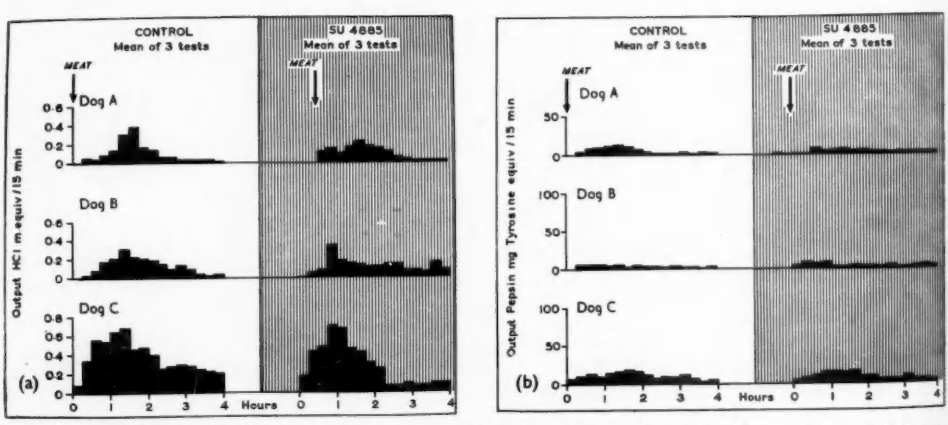


FIG. 1.—*The effect of SU 4885 (15 mg./kg. intravenously) on the outputs of* (a) *acid and* (b) *pepsin from Heidenhain pouches of the stomach stimulated by a meal of meat in three dogs.*

TABLE I

EFFECT OF SU 4885 ON OUTPUTS OF JUICE, ACID, AND PEPSIN FROM SEPARATED POUCHES IN THREE DOGS AFTER STANDARD MEAL

| Dog | Volume Juice (ml./4 hr.) | | Output Acid (mEq./4 hr.) | | Output Pepsin (mg. tyrosine/4 hr.) | |
|---|---|---|---|---|---|---|
| | Control | SU 4885 | Control | SU 4885 | Control | SU 4885 |
| A | 15·0 | 13·4 | 1·499 | 1·392 | 66·7 | 39·5 |
| B | 22·7 | 28·9 | 1·993 | 1·983 | 44·1 | 66·7 |
| C | 42·2 | 34·5 | 5·472 | 4·497 | 168·6 | 132·8 |

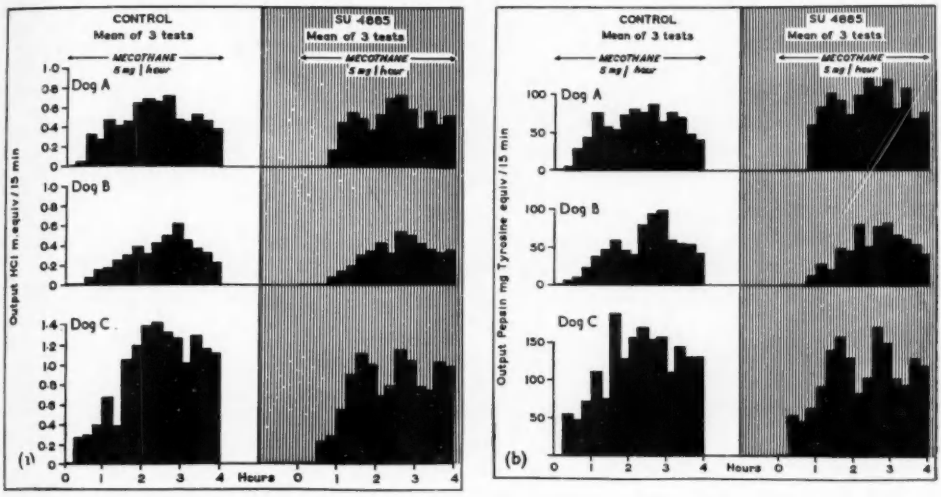


FIG. 2.—*The effect of SU 4885 (15 mg./kg. intravenously) on the outputs of* (a) *acid and* (b) *pepsin from Heidenhain pouches of the stomach stimulated by a continuous subcutaneous injection of "mecothane" (5 mg./hr.) in three dogs.*

TABLE II

EFFECT OF SU 4885 ON OUTPUTS OF JUICE, ACID, AND PEPSIN FROM SEPARATED POUCHES IN THREE DOGS STIMULATED BY CONTINUOUS SUBCUTANEOUS INFUSION OF MECOTHANE

| Dog | Volume Juice (ml./4 hr.) | | Output Acid (mEq./4 hr.) | | Output Pepsin (mg. tyrosine/4 hr.) | |
|---|---|---|---|---|---|---|
| | Control | SU 4885 | Control | SU 4885 | Control | SU 4885 |
| A | 57·5 | 54·5 | 6·708 | 6·286 | 869·8 | 1194·2 |
| B | 49·8 | 46·6 | 4·468 | 4·212 | 767·2 | 639·9 |
| C | 103·8 | 88·1 | 14·493 | 11·285 | 1859·6 | 1585·5 |

TABLE III

EFFECT OF SU 4885 AND CORTISOL ON SECRETION OF JUICE, ACID, AND PEPSIN FROM SEPARATED POUCHES IN THREE DOGS STIMULATED BY CONTINUOUS SUBCUTANEOUS INJECTION OF HISTAMINE ACID PHOSPHATE

| Dog | | Volume Juice (ml./15 min.) | | | | | | Output Acid (mEq./15 min.) | | | | | | Output Pepsin (mg. tyrosine/15 min.) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Control | | | SU 4885 | | | Control | | | SU 4885 | | | Control | | | SU 4885 | | |
| | | I* | II | III | I | II | III | I | II | III | I | II | III | I | II | III | I | II | III |
| Benefit | A | 4·4 | 5·0 | 5·0 | 4·9 | 4·7 | 4·9 | 0·603 | 0·684 | 0·700 | 0·653 | 0·596 | 0·605 | 8·7 | 10·1 | 11·8 | 11·2 | 9·1 | 11·9 |
| Response | B | 7·1 | 7·3 | 7·5 | 6·9 | 7·3 | 7·0 | 0·919 | 1·076 | 1·109 | 0·924 | 1·018 | 0·954 | 12·8 | 23·6 | 16·7 | 17·6 | 19·2 | 22·3 |
| Control | C | 6·6 | 6·7 | 6·1 | 6·4 | 7·2 | 6·5 | 0·996 | 1·028 | 0·929 | 0·881 | 1·012 | 0·930 | 26·2 | 29·5 | 24·0 | 39·9 | 37·9 | 29·1 |

*I = mean of six collections before SU 4885; II = mean of nine collections after SU 4885; III = mean of six collections after cortisol.

The absence of significant effect was confirmed by an analysis of variance of the mean logarithms of the outputs of juice, acid, and pepsin in the control tests in all three dogs and in these carried out after SU 4885.

*Response to Mecothane.*—The intravenous injection of SU 4885 (15 mg. per kg. body weight) was similarly without significant effect on the outputs of juice, acid, and pepsin secreted in response to a continuous subcutaneous infusion of "mecothane" (Fig. 2 and Table II). This also was confirmed by an analysis of variance of the logarithms of the outputs.

*Histamine.*—Neither the injection of SU 4885 (15 mg. per kg. body weight) nor that of cortisol (100 mg.) had any effect on the secretory response to a continuous subcutaneous infusion of histamine acid phosphate (25 $\mu$g. base/kg./hr.). The results of these tests are shown graphically in Fig. 3. The

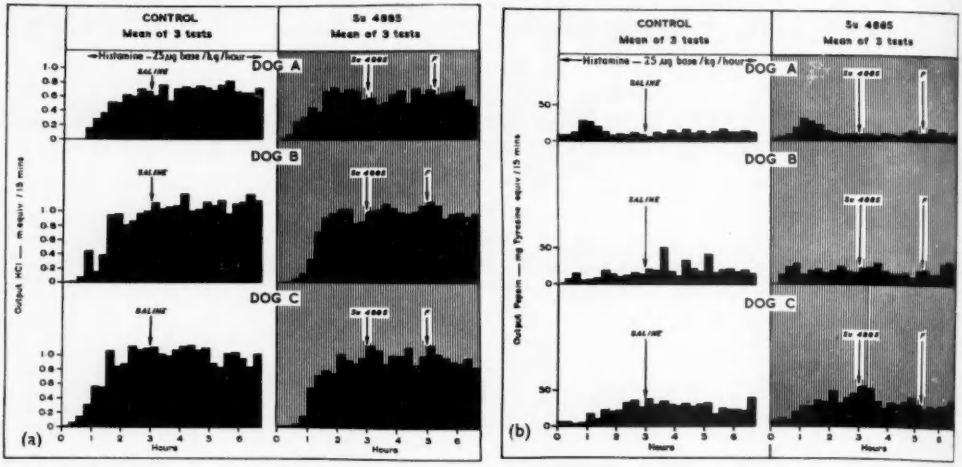


FIG. 3.—*The effect of SU 4885 (15 mg./kg. intravenously) and cortisol (100 mg. intravenously) on the outputs of* (a) *acid and* (b) *pepsin from Heidenhain pouches of the stomach stimulated by a continuous subcutaneous injection of histamine acid phosphate (or 25 mg. base/kg./hr.) in three dogs.*

mean outputs of juice, acid, and pepsin for six 15-minute collections before SU 4885 (Tables I-III), nine 15-minute collections after SU 4885 (Table II), and six 15-minute collections after cortisol (Table III) were calculated for each dog and compared with those of the corresponding periods of the control tests. No obvious difference was noted (Table III).

INGESTION OF SU 4885.—In three of the four dogs studied free acid was present in the gastric juice during the control period. In these three dogs the ingestion of SU 4885 resulted in a reduction in the output of acid from the Heidenhain pouch (Fig. 4 and Table IV). The difference between the means of the logarithms of the outputs of acid during the control period and that in which SU 4885 was ingested were statistically significant in each animal (Table V).

One of these three dogs died from peritonitis after retraction of the pouch during the experiment. In the other two dogs the acid output returned to the control level when SU 4885 was discontinued, and the difference between the outputs of acid during the period of SU 4885 ingestion and that following its withdrawal was again significant (Table V). The fourth dog had no free acid in its gastric juice during any phase of the experiment.

The inhibition of the output of acid was largely due to a reduction of concentration of acid in the secreted juice, and the slight reduction in the volume of juice in the three dogs which secreted free acid was insignificant. In the fourth dog (Dog F), which had no free acid in the gastric juice, the volume was increased during the period of SU 4885 administration.

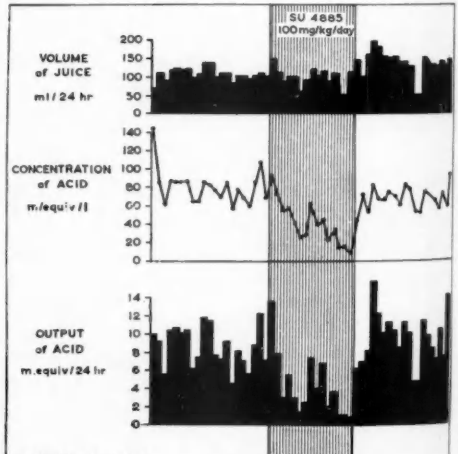


FIG. 4.—*The effect of oral ingestion of SU 4885 (100 mg./kg./day) on the daily outputs of juice, acid, and pepsin from a Heidenhain pouch of the stomach in a dog.*

TABLE IV

EFFECT OF SU 4885 ON 24-HOUR SECRETION FROM SEPARATED POUCHES IN FOUR DOGS

| Dog | SU 4885 | No. of Collections | Volume Juice (ml./24 hr.) | Concentration HCl (mEq./l.) | Output HCl (mEq./24 hr.) | Output Pepsin (mg. tyrosine eq./24 hr.) |
|---|---|---|---|---|---|---|
| D | Before | 21 | 113 | 77 | 9·1 | 517 |
| | During | 14 | 100 | 39 | 4·9 | 528 |
| | After | 19 | 141 | 64 | 9·5 | 659 |
| E | Before | 10 | 48 | 62 | 2·9 | 465 |
| | During | 15 | 47 | 39 | 1·9 | 435 |
| | After | 17 | 53 | 58 | 3·4 | 378 |
| F | Before | 21 | 34 | 0 | 0 | 248 |
| | During | 15 | 50 | 0 | 0 | 505 |
| | After | 18 | 44 | 0 | 0 | 213 |
| G | Before | 6 | 217 | 107 | 23·2 | 488 |
| | During | 7 | 184 | 84 | 15·7 | 763 |
| | After | — | — | — | — | — |

TABLE V

ANALYSIS OF ACID OUTPUTS

| Dog | SU 4885 | Mean Log. Acid Output | Mean Difference Log. | P |
|---|---|---|---|---|
| D | Before | 0·932 | 0·423 ± 0·045* | <0·001 |
| | During | 0·509 | | |
| | After | 0·954 | 0·445 ± 0·046 | <0·001 |
| E | Before | 0·437 | 0·170 ± 0·030 | <0·001 |
| | During | 0·267 | | |
| | After | 0·459 | 0·192 ± 0·081 | <0·05 |
| F | Before | — | — | — |
| | During | — | — | — |
| | After | — | — | — |
| G | Before | 1·350 | 0·169 ± 0·071 | <0·05 |
| | During | 1·180 | | |

* Standard error of means.

TABLE VI

ANALYSIS OF 24-HOUR VOLUME OF JUICE

| Dog | SU 4885 | Mean Volume Juice Dog (ml./24 hr.) | Mean Difference | P |
|---|---|---|---|---|
| D | Before | 2·035 | 0·053 ± 0·036 | >0·1 |
| | During | 1·982 | | |
| | After | 2·142 | 0·160 ± 0·037 | <0·01 |
| E | Before | 1·676 | 0·010 ± 0·027 | >0·7 |
| | During | 1·666 | | |
| | After | 1·688 | 0·022 ± 0·051 | >0·6 |
| F | Before | 1·519 | 0·173 ± 0·032 | <0·001 |
| | During | 1·692 | | |
| | After | 1·669 | 0·023 ± 0·027 | >0·3 |
| G | Before | 2·322 | 0·065 ± 0·060 | >0·3 |
| | During | 2·257 | | |
| | After | — | | |

TABLE VII

ANALYSIS OF 24-HOUR OUTPUT OF PEPSIN

| Dog | SU 4885 | Mean Output Pepsin (log. mg. tyrosine eq./24 hr.) | Mean Difference | P |
|---|---|---|---|---|
| D | Before | 2·631 | 0·050 ± 0·093 | >0·4 |
| | During | 2·681 | | |
| | After | 2·822 | 0·141 ± 0·095 | >0·1 |
| E | Before | 2·645 | 0·037 ± 0·073 | >0·6 |
| | During | 2·608 | | |
| | After | 2·549 | 0·059 ± 0·057 | >0·3 |
| F | Before | 2·347 | 0·309 ± 0·074 | <0·01 |
| | During | 2·656 | | |
| | After | 2·295 | 0·361 ± 0·077 | <0·01 |
| G | Before | 2·664 | 0·202 ± 0·077 | <0·05 |
| | During | 2·866 | | |

The output of pepsin, as is normal in denervated pouches, was low, and in none of the four dogs was it significantly reduced by SU 4885. In two dogs (Dogs F and G) the output of pepsin was increased while the drug was being taken (Table VII).

## DISCUSSION

It is clear from these experiments that the administration of SU 4885 by single intravenous injection is without effect on the immediate secretory response of canine Heidenhain pouches to the ingestion of meat or subcutaneous "mecothane" or histamine. However, when the drug was administered by mouth over a period of 10 to 14 days the 24-hour output of acid from Heidenhain pouches was decisively inhibited, this effect being due to a reduction in the concentration of acid in the gastric juice. The volume of juice and output of pepsin were not significantly influenced by SU 4885 administered in this way.

It is not possible to claim on this evidence that the effect of the drug is mediated by its properties to inhibit adrenocortical function, and in the absence of further supplies experimental proof of the nature of its action must necessarily be delayed. Nevertheless, certain similarities between the nature of its action and that of corticotrophin and cortisone provide circumstantial evidence that its action on

gastric secretory function is due to such a mechanism.

There is now considerable evidence that the prolonged administration of corticotrophin or cortisone stimulates the secretion of acid from Heidenhain pouches in dogs (Zubiran, Kark, and Dragstedt, 1952; Zubiran, Kark, Montalbetti, Morel, and Dragstedt, 1952; Villarreal, Ganong, and Gray, 1955; McGee, Blackburn, Lance, and Scott, 1959; Clarke, Neill, and Welbourn, 1960). Administration of these hormones over a shorter period of time is more uncertain in its effect (Ragins, Dragstedt, Landor, Lyon, and Dragstedt, 1956; Clarke *et al.*, 1960), and Clarke *et al.* found that it requires three to four days for stimulation.

A similar time-effect relationship was noted in our studies with SU 4885, and it was only with prolonged administration that an inhibitory action was revealed.

Both Villarreal *et al.* (1955) and Clarke *et al.* (1960) found that the effect of corticotrophin and cortisone on secretion from the Heidenhain pouch was primarily on the concentration of acid secreted, the volume being affected to a less extent. Other workers have found that the volume also may be increased (Zubiran *et al.*, 1952a and b; McGee *et al.*, 1959) although the large 24-hour volumes of juice collected from the pouches (249 to 750 ml.) are greatly in excess of those in this study and may more readily reflect a change. McGee *et al.* assumed from their *p*H records that the action of cortisone was mainly in the volume of juice secreted and that the concentration of acid was affected to a less extent. However, if the concentration of acid is calculated from their data it is found that during administration of cortisone it was increased from 106 to 136 mEq./l., a change which, although of little effect on the *p*H of the juice, is nevertheless in keeping with that described by others.

The action of SU 4885 in our dogs is again comparable, the reduction of acid output from the pouches being due mainly to a reduction in the concentration of acid in the secreted juice.

The effect of corticotrophin and cortisone on the secretion of pepsin from Heidenhain pouches of the stomach is less well documented. The findings of Villarreal *et al.* (1955) that this was markedly increased during corticotrophin administration were not confirmed by Clarke *et al.* (1960). Our finding that SU 4885 was without effect on the secretion of pepsin therefore is not evidence against its action on gastric secretion being secondary to adrenal depression of cortisol secretion.

It is concluded that the adrenal inhibitor SU 4885, administered over a prolonged period, inhibits the secretion of acid from canine Heidenhain pouches. The nature of its action must meantime remain obscure although it appears reasonable to suppose that it is mediated by adrenocortical inhibition.

## SUMMARY

The action of the adrenocortical inhibitor, SU 4885, has been studied in dogs with separated pouches of the stomach of Heidenhain type.

In the first group of experiments in three dogs the drug was given by single intravenous injection during the secretory response to (1) ingestion of a meal of meat, (2) subcutaneous mecothane, and (3) subcutaneous histamine. No effect was noted.

In the second group of experiments the drug was given orally for seven to 15 days to four dogs on a constant diet and juice collected serially every 24 hours. Under these conditions SU 4885 reduced the secretion of acid from the stomach pouches.

We wish to thank Professor C. F. W. Illingworth, in whose department this work was carried out, for his help. Professor R. C. Garry kindly allowed us to house the dogs in the Institute of Physiology in the University of Glasgow and we are grateful to him and to his animal house technicians for their assistance. The SU 4885 was supplied by Ciba Laboratories Ltd., and we are grateful to Dr. C. D. Falconer for his cooperation.

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# INTRAOESOPHAGEAL ADENOCARCINOMA

BY

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A study of 87 cases of carcinoma involving the gastro-oesophageal region included seven cases of adenocarcinoma confined to the anatomical limits of the oesophagus. Six of these intraoesophageal adenocarcinomas appear to have arisen in "oesophagi lined by columnar epithelium". The seventh, a carcinoma of double histological pattern associated with a sliding hiatus hernia, showed a complex mixture of epithelial structures in the lower oesophagus. The histogenesis of intraoesophageal adenocarcinoma is discussed, and it is stressed that its prognosis may be relatively favourable.

Adenocarcinoma of the oesophagus, once thought to be a very rare lesion, has been reported more frequently in recent years. Smithers (1956) recorded a total of 21 cases. There has been much controversy as to the histogenesis of these tumours, as there has also been with regard to the glandular epithelium sometimes found in the oesophagus.

In the course of a study of 87 cases of gastro-oesophageal carcinoma, 11 adenocarcinomas situated mainly or entirely within the oesophagus were encountered, and it is with some of these that this communication mainly deals. The results of the investigation of the series of gastro-oesophageal carcinomas will first be summarized.

The study comprised 87 surgically-excised carcinomas of the gastro-oesophageal region. The anatomical and histological features of the tumours are shown in Table I. Adenocarcinomas are the largest histological group in each anatomical category; they outnumber squamous carcinomas even in the mainly intraoesophageal group. No squamous carcinomas were found in the group astride the junction or in the mainly intragastric tumours. It is clear that the tissues of the oesophageal wall offer a favourable pathway for the spread of gastric carcinoma; the gastric wall, however, is evidently not a favourable environment for oesophageal carcinoma. Anaplastic carcinomas occurred on both sides of the junction. The mixed carcinomas, a heterogeneous group, are being fully described elsewhere (Dodge, 1961). They included two adenocarcinomas showing squamous metaplasia, two muco-epidermoid carcinomas (probably arising in oesophageal mucous glands), two carcinomas, probably of double histogenesis, and one "collision carcinoma" arising from the meeting of two separate invasive growths. The tumour was localized in 14 of the 66 adenocarcinomas, two of the mixed carcinomas, but in none of the anaplastic or squamous carcinomas. Twenty cases came to necropsy, and in 15 there was no evidence of metastasis. Metastases are known to have occurred in 15 cases (10 adenocarcinomas, one squamous, one anaplastic, and three mixed carcinomas). Metastases were confined to the regional lymph nodes, ribs and chest wall, liver, adrenals, and lungs. Twenty-one patients died within one month of operation; 16 are known to have survived one year. Only one patient (with a squamous carcinoma) had so far survived five years.

Of the 11 adenocarcinomas situated mainly or entirely within the oesophagus, four were situated

TABLE I

SITUATION AND HISTOLOGICAL TYPES OF GASTRO-OESOPHAGEAL CARCINOMA

| Histological Type | Anatomical Situation | | | Total |
|---|---|---|---|---|
| | Mainly Intraoesophageal | Astride Gastro-oesophageal Junction | Mainly Intragastric | |
| Adenocarcinoma | 11 | 16 | 39 | 66 |
| Squamous carcinoma | 7 | 0 | 0 | 7 |
| Anaplastic carcinoma | 2 | 0 | 5 | 7 |
| Mixed carcinoma | 5 | 1 | 1 | 7 |

TABLE II
INTRAOESOPHAGEAL ADENOCARCINOMA

| Case | Sex | Age | Area Involved by Tumour | Post-operative Course |
|---|---|---|---|---|
| 1 | M | 66 | 7·5 cm. of lower oesophagus | Died 16 months later of pneumonia. No recurrence or metastasis |
| 2 | M | 60 | Lower third of oesophagus | Died 1 yr. later. No recurrence or metastasis |
| 3 | M | 54 | Lower third of oesophagus | Well 1½ yr. later |
| 4 | M | ? | 3 cm. of lower oesophagus | Post-operative death. No metastasis |
| 5 | M | 41 | 5 cm. of middle third of oesophagus | Recurrence 13 months later. Died 19 months later. |
| 6 | M | 59 | 7·5 cm. of lower oesophagus | Well 2½ yr. later |
| 7 | M | 65 | Mass in lower third of oesophagus | Post-operative death (pulmonary embolism). No metastases |

partly within the proximal part of the stomach, and there is little doubt that these were gastric adenocarcinomas which had spread almost entirely upward into the oesophagus. Seven cases of intraoesophageal adenocarcinoma were found, and it is with these that the present study is mainly concerned. In these cases, the tumour was limited to the anatomical oesophagus, and the stomach was intact. Details of these cases are summarized in Table II.

The extent to which the oesophagus may be invaded by gastric carcinoma is well recognized. In two of the partly intragastric neoplasms the tumour extended from the stomach to the level of the aortic arch. If an oesophageal biopsy from a case of suspected oesophageal cancer reveals adenocarcinoma, it is sometimes assumed that this indicates that a gastric carcinoma has invaded the oesophagus, and that the patient is therefore probably beyond surgical aid. One of the purposes of the present paper, however, is to reiterate the fact that adenocarcinomas limited to the oesophagus do occur, and that, as Barrett (1957) has pointed out, the prognosis of adenocarcinoma within the oesophagus need not be hopeless.

Details of the seven cases are shown in Table II. The following points are stressed: (1) In each of these cases the tumour, as seen at operation and in the gross specimen, lay entirely within the oesophagus. (2) In Cases 1-6 inclusive, the tumours were bounded at their lower ends by columnar epithelium (Case 7 is discussed in more detail below). (3) In these six cases, the columnar cell glandular epithelium extended from the stomach in a continuous sheet into the oesophagus up to the tumour margin. (4) In six of the seven cases the tumours were situated in the lower third of the oesophagus. The most proximally-placed adenocarcinoma (Case 5) had its lower margin 4 cm. above the diaphragm. (5) In Case 5 the tumour extended to the proximal margin of resection; in the other six cases the upper margin of the tumour was bounded by squamous epithelium. (6) In Cases 1-6 inclusive, there was no evidence of a diaphragmatic defect or hiatus hernia, and the gross topography of the gastro-oesophageal region appeared to be normal at the time of operation. Several of these features are seen in Fig. 1. These findings lead to the conclusion that Cases 1-6 are each an example of an adenocarcinoma that has arisen in a "lower oesophagus lined by columnar epithelium", as described by Barrett (1958).

Case 7 revealed a more involved state of affairs, with a hiatus hernia, a complex mixture of epithelial structures below the tumour margin, and a carcinoma showing two distinct structural patterns. This case will be described in more detail.

### CASE HISTORY

A man of 65 complained of retrosternal pain, worse on eating, for two months. He had no difficulty in swallowing. A barium swallow revealed a filling defect in the lower third of the oesophagus, and below this a reducible, sliding hiatus hernia, with evidence of reflux.

FIG. 1.—*Diagram of a longitudinal whole-tumour section of an adenocarcinoma lying within the lower third of the oesophagus (Case 3). Squamous epithelium shaded black, columnar epithelium vertically hatched, tumour unshaded. Muscularis diagonally hatched, other tissue stippled. Extensive ulcerated carcinoma, with an outlying "satellite" nodule of tumour at the proximal margin of resection (A).* × 2·5.

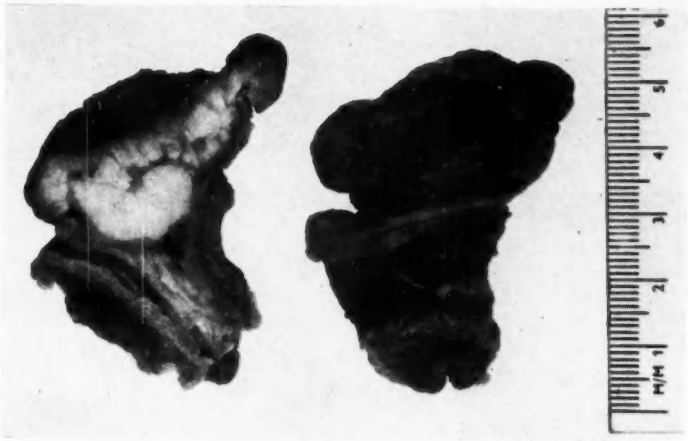

FIG. 2.—*Case 7. Polypoid carcinoma of oesophagus. Specimen removed by gastro-oesophageal resection, seen from the outside (right) and in longitudinal section (left). At the right, the tumour protrudes through the upper everted end of the specimen, and there is a rim of gastric mucosa at the lower end. At the left, the tumour is seen to lie in the submucosa of the oesophagus.*

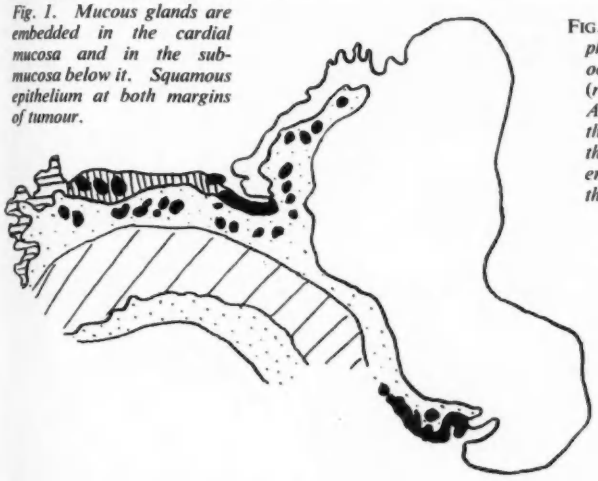

FIG. 3.—*Case 7. Diagram of longitudinal section of the specimen. Oesophageal squamous epithelium and oesophageal mucous glands are shaded black, fundal mucosa horizontally, and cardial mucosa vertically hatched. Tumour unshaded, and other tissues as in Fig. 1. Mucous glands are embedded in the cardial mucosa and in the submucosa below it. Squamous epithelium at both margins of tumour.*

Oesophagoscopy showed a tumour at 37 cm. from the incisors. At operation a tumour was found in the lower oesophagus; it was described as lying about 4·5 cm. above the gastro-oesophageal junction. The tumour was excised, with a margin of normal-looking tissue above and below, including a cuff of cardial mucosa, and a gastro-oesophageal anastomosis was performed. Three weeks later the patient died suddenly. Necropsy revealed ilio-femoral venous thrombosis and a massive pulmonary enbolus. There was no evidence of residual tumour or of secondary deposits.

The outer and cut surfaces of the operation specimen are shown in Fig. 2. The large fungating tumour lies well within the oesophageal tube. Figs. 3 and 4 show diagrammatically the state of affairs revealed by microscopy. The important features are: (1) A short length of gastric mucosa of fundal type at the distal margin; (2) a strip of gastric mucosa of cardial type extending upwards along the oesophageal tube, almost to the distal margin of the tumour, but separated from it by a short zone of squamous epithelium; (3) several glands within the strip of cardial mucosa showing intestinal metaplasia (Fig. 5); (4) islands of squamous epithelium also embedded in the same strip (Fig. 5); (5) numerous oesophageal mucous glands in the submucosa beneath the cardial-type epithelium (Fig. 6); (6) an adenocarcinoma, bounded above and below by squamous epithelium, showing two distinct and quite sharply separated types of growth: (*a*) a well-differentiated adenocarcinoma, confined to the surface, at both upper and lower margins of growth (Fig. 7), (*b*) a much less differentiated adenocarcinoma (Fig. 8), forming the main bulk of the tumour, and penetrating the oesophageal submucosa more deeply.

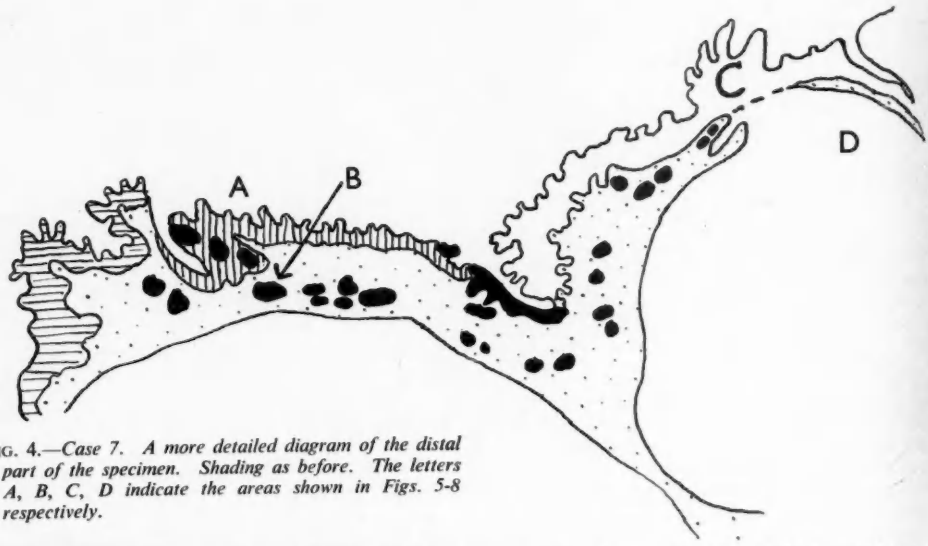


FIG. 4.—*Case 7. A more detailed diagram of the distal part of the specimen. Shading as before. The letters A, B, C, D indicate the areas shown in Figs. 5-8 respectively.*

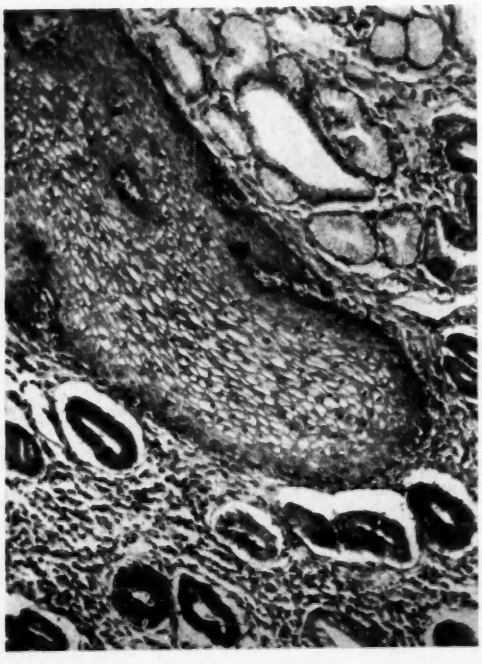

FIG. 5.—*Case 7. Area A of Fig. 4. An island of squamous epithelium in the cardial mucosa. Many of the glands* (L.) *show intestinal metaplasia. Haematoxylin and eosin* × *100.*

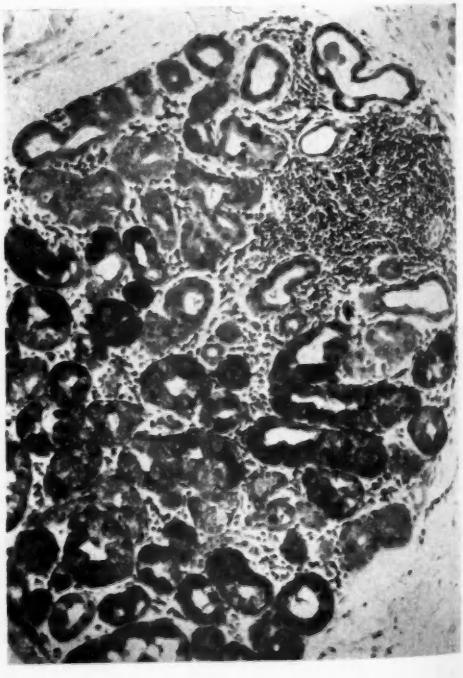

FIG. 6.—*Case 7. Area B of Fig. 4. Oesophageal mucous gland in submucosa below cardial mucosa. Haematoxylin and eosin* × *100.*

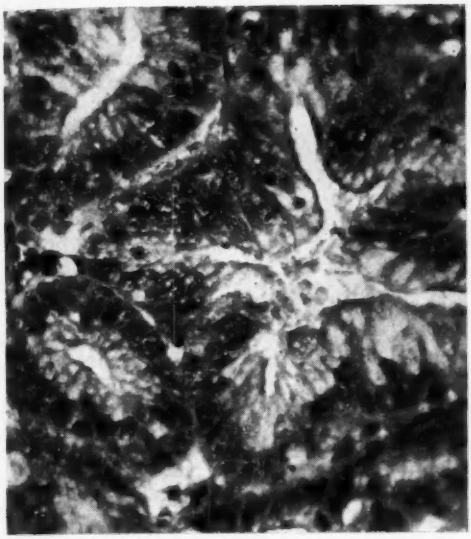

FIG. 7.—*Case 7. Area C of Fig. 4. Well-differentiated adenocarcinomatous pattern in superficial, peripheral part of tumour. Haematoxylin and eosin × 330.*

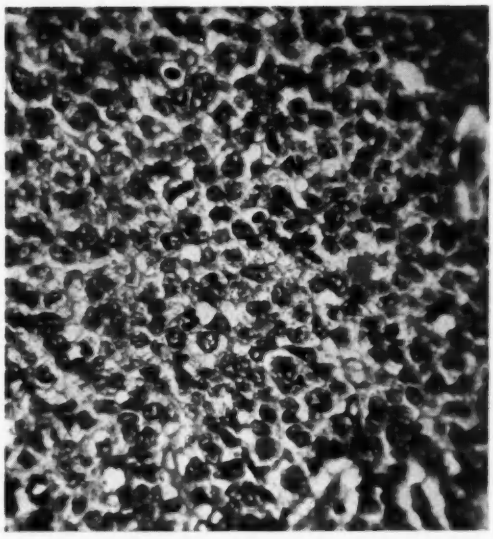

FIG. 8.—*Case 7. Area D of Fig. 4. Poorly-differentiated carcinoma forming central, deeper part of tumour. Haematoxylin and eosin × 330.*

The cardial mucosa here is evidently of a different origin from the mucosa seen in the "oesophagus lined by columnar epithelium". Oesophageal mucous glands and islands of squamous epithelium were not seen in the glandular epithelium below the tumours in Cases 1-6. The intestinal metaplasia in this area is also unusual. The dual histological structure of the carcinoma suggests the possibility of a double origin. The superficial marginal zone of well-differentiated adenocarcinoma may have arisen from another area of glandular epithelium (either of cardial or perhaps of intestinal type). The situation of the more deeply-placed central mass of less differentiated carcinoma suggests that it may have arisen from deeper structures, possibly from mucous glands in the submucosa. The mucous glands, abundant more distally, are absent around the tumour area, and the possibility that this component of the tumour has arisen in oesophageal mucous glands cannot be excluded.

## DISCUSSION

All these tumours lay within the confines of the oesophagus, as seen at operation, *i.e.*, within the tube-shaped structure, devoid of a serosal coat, leading from the pharynx to the sac of the stomach. In Cases 1-6 there was no evidence of a diaphragmatic defect or of any downward extensions of the peritoneal cavity. In each of these cases, however, the tumour was found to be bordered below by columnar epithelium, which extended in an apparently unbroken sheet distally from the tumour edge. Proximally, the tumours were bordered by oesophageal squamous epithelium. The tumours in Cases 1-4 and Case 6 lay in the lower third of the oesophagus and in Case 5 in the middle third. These findings indicate that each of these six carcinomas has arisen in what Barrett (1958) calls "the lower oesophagus lined by columnar epithelium". In this condition, which is probably a malformation rather than an acquired defect, columnar epithelium extends upwards from the stomach in a continuous sheet into an oesophagus which is in all other respects normal. This malformation differs from a sliding hiatus hernia in that the anatomy of the peritoneal sac and the local arteries remains normal. It is therefore easy to understand how its existence may be overlooked both by surgeons and pathologists.

The remaining case (Case 7) shows a more complicated pattern. This was the only case in which a sliding hiatus hernia was reported. The situation revealed here (Figs. 2-8) may be interpreted as follows:

(1) The strip of gastric mucosa at the lower end of the specimen represents the upper limit of the herniated stomach. (2) The strip of cardiac-type mucosa above this, in which were embedded islands of squamous epithelium and below which lay oesophageal mucous glands, has come about as a consequence of reflux oesophagitis. This mixture of epithelial types was not seen in any of the other cases, and it is suggested that in this case, where there was reflux of gastric contents, the original squamous epithelium had been largely destroyed and replaced by upward-growing columnar epithelium, and had survived only in isolated patches. The protected mucous glands have, however, remained intact, and they label this segment as "oesophagus". (3) The carcinoma, bounded at its lower (as well as upper) margin by a narrow zone of squamous epithelium, may have arisen from a further island of proliferating columnar epithelium, but could also be of mucous gland origin. (4) The double histological structure of the carcinoma indeed raises the possibility of a double histogenesis. The well-differentiated, superficial, peripheral component may have arisen from columnar epithelium lining the lumen of the oesophagus. The poorly-differentiated, deeply placed, central component may have arisen from mucous glands in the submucosa. It may be significant that oesophageal mucous glands are numerous both above and below the tumour, but are absent along its deep border.

One other possible origin of intraoesophageal adenocarcinoma should be mentioned, namely, the islands of so-called heterotopic gastric mucosa in the oesophagus, described by Schridde (1904), Taylor (1927), and Rector and Connerley (1941). The work of Johns (1952) on the development of the oesophageal lining has made it clear that these islands represent, not ectopic gastric mucosa, but the persistent remains of the normal oesophageal lining of the foetus. He showed that squamous transformation begins at the mid-oesophagus and that the extremities of the organ are the last to lose their columnar epithelium. This explains why these "heterotopic" islands appear at the upper and lower ends of the oesophagus. No ulceration has been described in connexion with these islands of glandular mucosa (Barrett, 1950), and only one well-documented case of adenocarcinoma of the upper oesophagus has been reported (Carrie, 1950). These islands are clearly a different abnormality from the lower oesophagus lined by columnar epithelium and from the state of affairs shown by Case 7.

Adenocarcinomas confined to the oesophagus are clearly an entity to be reckoned with. The post-operative course of the seven cases reported here justifies their separation from those of gastric carcinoma invading the oesophagus. None of the patients has shown evidence of metastasis. In six of the seven cases complete surgical excision appears to have been achieved; five patients survived the operation for a year, and the two who died within a year of operation had no evidence of local recurrence or metastasis at necropsy. These results suggest that when a patient is found by biopsy to have adenocarcinoma in the oesophagus, it may be well worth while to try to determine whether this is an oesophageal extension of a gastric carcinoma, with a very poor prognosis, or whether it represents an intraoesophageal adenocarcinoma. In the latter case, surgical excision may well be feasible. As more of these lesions become available for study, further information on their histogenesis and behaviour may come to light.

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*New Methods for Diagnosis and Research*

# PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY

BY

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This is an evaluation of percutaneous transhepatic cholangiography, a technique of over eight years' standing, previously considered by many authorities as both unrewarding and dangerous. The value and risks of the procedure have been examined in 20 patients with obstructive jaundice of uncertain origin and in one further patient with a post-cholecystectomy syndrome. The presence and the nature of extrahepatic obstructive lesions was correctly diagnosed in 10 of 11 patients shown to have this cause for jaundice. The failure to obtain cholangiograms in the remaining 10 patients was correctly correlated with the presence of intrahepatic obstructive disease due to hepatitis or primary biliary cirrhosis. The risks of percutaneous cholangiography seem over-rated, biliary peritonitis occurring in under 5% of patients submitted to the procedure.

Cholangiography by means of intravenously administered agents is rarely successful in the presence of deep jaundice, and laparotomy, with or without operative cholangiography, is usually required to demonstrate the site and nature of obstructive lesions in the bile passages. In recent years attempts have been made to opacify the biliary tree by direct percutaneous injection of contrast medium. This was achieved by Royer and Solari (1947) who injected dye into the gall-bladder under direct vision at peritoneoscopy. Although they considered the risk of leakage of bile to be small, fear of this complication led others to use the transhepatic route. Kapandji (1950) punctured the gall-bladder, previously opacified by giving pheniodol, under fluoroscopic control using the percutaneous transhepatic approach. Cholangiography by means of percutaneous puncture of the intrahepatic biliary tree had in fact been described by Huard and Do-Xuan-Hop as long ago as 1937. They punctured the intrahepatic biliary tree in three patients with extrahepatic biliary obstruction and injected "lipiodol" into two of these, thus demonstrating dilatation of the bile passages. In 1952, Carter and Saypol's paper aroused general interest in this technique and since then a number of reports of percutaneous transhepatic cholangiography have appeared (Table II), chiefly in the South American and French literature.

Kidd (1956) enumerated four indications for the procedure: first, to investigate the cause of biliary symptoms after cholecystectomy, secondly to diagnose the presence and site of a carcinoma of the biliary system, thirdly to demonstrate the site of calculous disease, and lastly directly to measure biliary pressure. Remolar, Katz, Rybak, and Pellizari (1956) considered the technique to be of value in the diagnosis of jaundice of doubtful aetiology, to differentiate calculus from carcinomatous biliary obstruction, and to investigate jaundice following cholecystectomy. However, percutaneous transhepatic cholangiography has not as yet gained general acceptance, principally because many clinicians fear the risk of causing biliary peritonitis.

We considered that the results previously reported were sufficiently encouraging to warrant a further reappraisal of the procedure, and this report deals with 21 patients in whom percutaneous transhepatic cholangiography has been performed.

## Technique

The procedure can conveniently be carried out in the *x*-ray department under local anaesthesia with 2% lignocaine B.P. In children or adults who are uncooperative, general anaesthesia with tracheal intubation and controlled respiration is to be preferred.

With the patient lying supine, a short bevelled needle, 12 cm. in length and of 1 mm. bore with a 20 ml. syringe containing saline attached, is introduced through the abdominal parietes at a point 2-4 cm. below and to the right of the xiphisternum. The needle is inclined in a slightly cephalad direction. An increased resistance can be felt when the needle enters the liver and, at this point if general anaesthesia is being used, respiration is controlled, or if under local anaesthesia, the patient is asked to breathe shallowly. The needle is then cleared

by injecting a few millilitres of saline and slowly advanced 6-8 cm., exerting constant suction with the syringe. It is then cleared again by injecting saline and slowly withdrawn, again applying suction. Entry into a bile passage is indicated by the aspiration of bile or white bile (mucus) into the syringe. To facilitate the detection of bile the syringe should contain clear saline and if penetration of a blood vessel causes this to become bloodstained, it should be replaced. Good lighting is essential and the procedure is best carried out in daylight to enable the brown coloration of the bile to be recognized. On one occasion deeply bile-stained ascitic fluid was aspirated and was mistaken for true bile. If no bile passage is penetrated this procedure is repeated, inclining the needle towards the right side, and if still unsuccessful a third attempt is made, this time inclining the needle towards the left. In one patient, after failure to penetrate a bile duct by this approach, puncture in the mid-axillary line was successful.

If a duct is entered aspiration is continued until no further bile can be obtained and the material sent for microscopy and culture. At this point it is essential that breathing be controlled since it is extremely easy accidentally to withdraw the needle from the duct or alternatively to tear the liver capsule. Then 10-20 ml. of 85% "hypaque" (Winthrop) is injected under fluoroscopic control if this is available. Films are taken as the contrast medium spreads throughout the biliary tree and filling of the lower part of the common duct may be facilitated by tilting the patient feet downwards. At this juncture barium may be given by mouth to outline the duodenum (Remolar *et al.*, 1956) thus obtaining an indication of the extent of any suprapapillary blockage of the duct. However, if barium is given great care is necessary to avoid obscuring detail of the lower end of the common duct.

The initial high density of contrast medium in the common duct provides a clear-cut picture of the biliary tree but may obscure filling defects. For this reason further films are taken over the next four to eight hours as the density of the contrast medium is diminishing.

Patients are placed on a hourly pulse chart for 24 hours after this procedure and the abdomen is carefully examined should the pulse rate rise or abdominal pain occur.

## Results

Of the 21 patients investigated by this technique, all except one were suffering from jaundice of the obstructive type. The remaining patient complained of attacks of severe upper abdominal pain following cholecystectomy. The final diagnosis in each patient is shown in Table I. In 11 patients a biliary radical was entered and contrast medium injected into the biliary tree; in the remaining 10 patients a bile duct was not encountered.

In each of the 11 patients in whom cholangiograms were obtained, an extrahepatic obstructive lesion was demonstrated to be the cause of the jaundice. The common duct was considerably dilated, varying between 1·2 and 2·5 cm. in width, and the intrahepatic biliary tree was also distended.

TABLE I
CLINICAL SUMMARY

| Case No. | Sex | Age | Duration of Jaundice in Months | Cholangiographic Findings | Cholangiographic Diagnosis | Operative Findings |
|---|---|---|---|---|---|---|
| 1 | F | 77 | 24 | Filling defects in common duct | Stones | Stones in common duct |
| 2 | F | 62 | 3 | Dilated common duct with no filling defects in 10 min. film | Carcinoma of pancreas | Stones in common duct |
| 3 | F | 55 | 1½ | Single filling defect in dilated common duct | Stones | Stones in common duct |
| 4 | M | 80 | 1 | Multiple filling defects in dilated common duct | Stones | Stones in common duct |
| 5 | F | 65 | 2 | Dilatation of ducts of right lobe with no filling of remainder of biliary tree | Carcinoma at porta hepatis | Carcinoma of bile duct at porta hepatis |
| 6 | M | 80 | 3 | Dilatation of whole biliary tree | Carcinoma of pancreas | Carcinoma of pancreas at necropsy |
| 7 | F | 35 | 2 | ,, | ,, | ,, |
| 8 | F | 60 | 1½ | ,, | ,, | ,, |
| 9 | F | 62 | 2 | ,, | ,, | ,, |
| 10 | M | 65 | 1 | ,, | ,, | ,, |
| 11 | F | 62 | 1½ | ,, | ,, | ,, |
| 12 | M | 50 | 5 | Negative | — | Cholangiolytic hepatitis |
| 13 | F | 35 | 3 | ,, | — | ,, |
| 14 | M | 58 | 3 | ,, | — | ,, |
| 15 | M | 22 | — | ,, | — | Neonatal hepatitis |
| 16 | M | 45 | 4 | ,, | — | Primary biliary cirrhosis |
| 17 | F | 52 | 12 | ,, | — | ,, |
| 18 | F | 36 | 24 | ,, | — | ,, |
| 19 | F | 57 | 60 | ,, | — | ,, |
| 20 | F | 55 | 1½ | ,, | — | Massive infiltration of liver by malignant melanoma at necropsy |
| 21 | F | 53 | — | ,, | — | No operation, eventual diagnosis post-cholecystectomy syndrome |

In the majority of patients the contrast medium diffused throughout the biliary tree filling the gall-bladder and cystic duct. Emptying into the duodenum was delayed and the dye could sometimes be detected in the biliary tree next day. In several patients the obstruction appeared to be complete and in these the dye was presumably reabsorbed into the blood stream.

The nature of the obstructive lesion was diagnosed correctly in 10 of the 11 patients in whom cholangiography was successful (Table I).

STONES IN THE COMMON DUCT.—These were identified as filling defects in the common duct shadow in three patients. In a fourth patient common duct stones were obscured by the initial density of the contrast medium and no subsequent films were obtained, the diagnosis being incorrectly presumed to be carcinoma of the pancreas. After this experience it was decided to take serial films at intervals following the injection and these on two occasions revealed filling defects due to calculi which had not been apparent in the initial films (Figs. 2, 3, and 4).

CARCINOMA OF PANCREAS.—This was diagnosed correctly in each of the seven patients in whom carcinoma was subsequently found at laparotomy. No characteristic deformity of the lower end of the common duct could be identified. The degree of dilatation of the biliary passages might be expected to be greater in patients with neoplastic obstruction than in those with common duct stones. However, no such difference was detectable in this series, and it appears that the diameter of the ducts is of little diagnostic value in deciding the cause of the obstruction in the individual patient. The diagnosis of carcinoma of the head of the pancreas has been made by demonstrating rapid filling of the biliary tree and common duct without emptying into the duodenum. Serial films are essential to exclude an intraluminal cause of obstruction.

CARCINOMA OF BILE DUCTS.—Carcinoma of the bile ducts at the porta hepatis was present in one patient in whom the correct diagnosis was made by cholangiography (Fig. 6).

In the 10 remaining patients the examination was abandoned after failure to penetrate a bile passage. Because of continuing jaundice of uncertain aetiology, nine of these patients underwent laparotomy and liver biopsy. In each the site of obstruction proved to be intrahepatic (Table I); the final diagnosis was primary biliary cirrhosis in four, cholangiolytic hepatitis in three, neonatal hepatitis in one, and massive infiltration of the liver with melanomatous deposits in one. The tenth patient, who suffered from attacks of severe upper abdominal pain following cholecystectomy and was not jaundiced, showed normal histological appearances on needle liver biopsy and has not been investigated further.

## ILLUSTRATIVE CASES

CASE 3.—M.B. was a woman aged 55.

*History.*—Jaundice, intermittent pain in the right loin, and malaise began six weeks before admission to hospital. She had previously had an attack of jaundice at 15 years of age. Physical examination revealed deep jaundice and a liver palpable two fingerbreadths below the right costal margin. Biochemical tests indicated that the jaundice was obstructive in nature, the alkaline phosphatase being 37 units and serum bilirubin 6·2 mg. %. A straight radiograph of the abdomen showed a single calcified opacity overlying the right renal shadow (Fig. 1).

*Transhepatic Cholangiography.*—Immediate biliary puncture was obtained and bile aspirated. Injection of 85% "hypaque" demonstrated a dilated common duct, the lower end of which appeared normal. At 10 minutes the opacity seen in the straight film was obscured (Fig. 2) but in the 20- and 30-minute films it was revealed as a

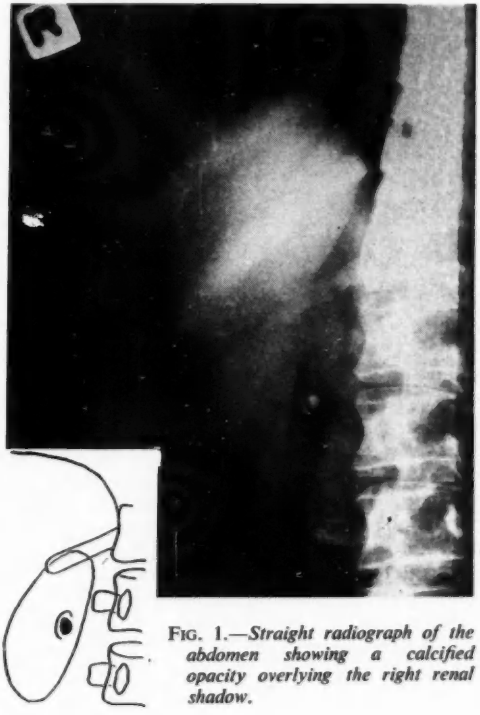

FIG. 1.—*Straight radiograph of the abdomen showing a calcified opacity overlying the right renal shadow.*

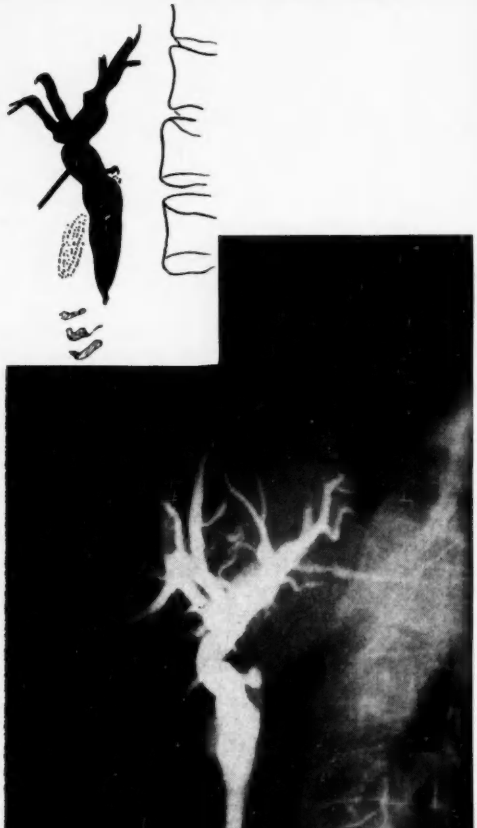

FIG. 2

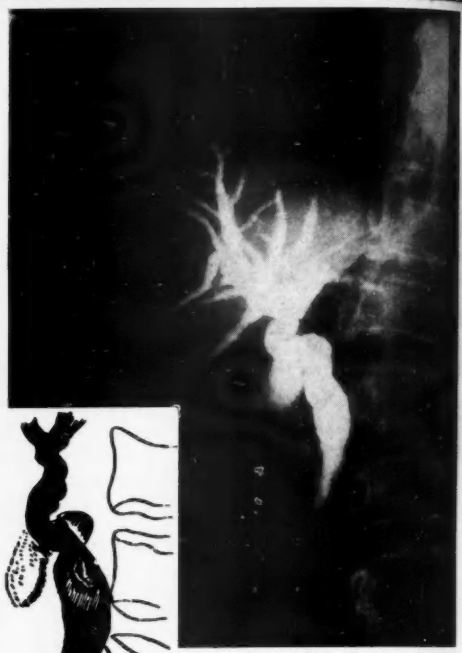

FIG. 3

FIG. 4

FIG. 2.—*Film taken 10 minutes after the injection of "hypaque" showing dilatation of the biliary tree, with medium passing into the duodenum.*

FIG. 3.—*Twenty-minute film showing the gall-bladder beginning to fill. A filling defect is now apparent in the common duct.*

FIG. 4.—*Thirty-minute film showing with greater clarity the filling defect in the common bile duct. The appearance of the gall-bladder in this film suggests cholelithiasis but no gall stones were present in the gall-bladder.*

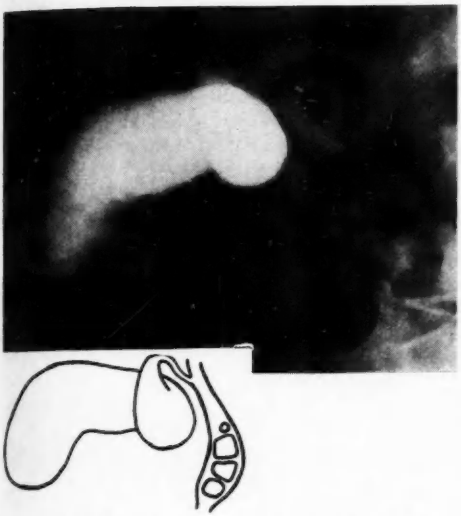

FIG. 5.—*Radiograph showing a large gall-bladder and a dilated common bile duct in which several filling defects can be identified, indicating a column of faceted stones.*

negative filling defect in the common bile duct (Figs. 3 and 4). The presence of contrast medium in the duodenal loop demonstrated that the obstruction was incomplete. The diagnosis was confirmed by subsequent laparatomy when a single cholesterol stone was removed from the common bile duct.

CASE 4.—R.J. was a man aged 80.

*History*.—After being jaundiced and febrile for several days he was admitted to hospital in a semi-comatose condition. He had had an episode of fever and jaundice four months previously which had subsided after several weeks' conservative treatment.

Examination revealed moderate jaundice, foetor hepaticus, and a flapping tremor. The liver was enlarged to two fingerbreadths below the costal margin.

A diagnosis of cholangitis was made and treatment with broad-spectrum antibiotics and dietary protein restriction led to a striking response and improvement in the jaundice.

*Transhepatic Cholangiography*.—This, performed six weeks after admission, revealed a dilated biliary tree. Although not apparent on the initial film, a column of faceted gall stones was visible in the common duct in the 60 min. film (Fig. 5).

CASE 5.—N.H. was a woman aged 65.

*History*.—Ten days after an influenzal-like illness jaundice developed . On admission to hospital six weeks later she was deeply jaundiced with moderate ascites. Liver function tests did not help to decide whether the jaundice was parenchymatous or obstructive in type, the serum bilirubin being 12 mg.% and the alkaline phosphatase 32 units. Liver biopsy indicated biliary obstruction showing bile thrombi, bile duct proliferation, and bile lakes.

*Transhepatic Cholangiography*.—This (Fig. 8) was performed after eight weeks of jaundice; a bile passage was entered with ease but only "white bile" was aspirated. After 7 ml. of bile had been removed 10 ml. 85% "hypaque" was injected against increasing resistance. Subsequent films showed dilatation of the right hepatic ducts only and extravasation of the contrast medium into the hepatic substance. A tentative diagnosis of carcinoma of the porta hepatis was made and subsequent laparotomy revealed a mass of malignant tissue obstructing the biliary tree at the junction of the right and left hepatic ducts and compressing the portal vein.

CASE 6.—H.S. was a man aged 80.

*History*.—He was admitted complaining of vague upper abdominal pain, constipation, anorexia of three months' duration. Examination revealed a jaundiced and wasted elderly man whose liver was enlarged to three fingerbreadths below the costal margin. Liver function tests suggested biliary obstruction, the serum bilirubin being 9·4 mg.% and alkaline phosphatase 94 units.

FIG. 6.—*Radiograph showing dilatation of the biliary tree. The common bile duct has a crenated outline which was not seen on all films, suggesting that it was due to muscular contraction.*

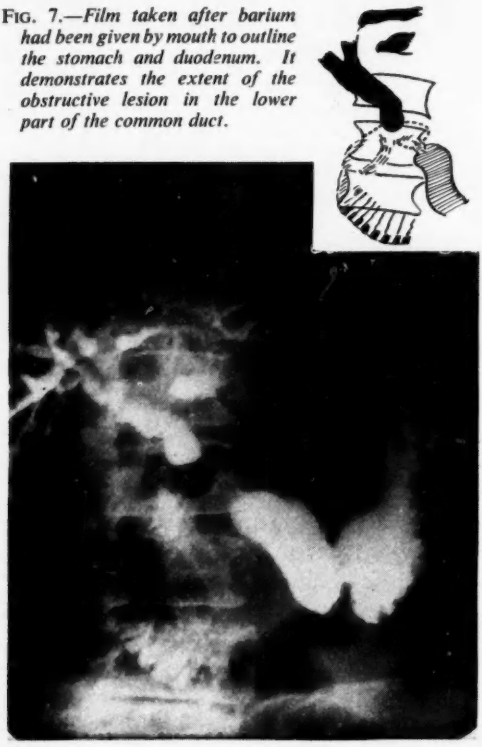

FIG. 7.—*Film taken after barium had been given by mouth to outline the stomach and duodenum. It demonstrates the extent of the obstructive lesion in the lower part of the common duct.*

*Transhepatic Cholangiography*.—Biliary puncture was easily accomplished and after aspiration of golden bile 20 ml. of "hypaque" was injected. The intrahepatic biliary tree and upper part of the common duct appeared dilated, the latter having a rather crenated outline (Fig. 6).

Barium suspension was later given by mouth to outline the stomach and duodenum (Fig. 7) where it will be seen that the block extends well up the common duct. A diagnosis of carcinoma of the pancreas was made.

Subsequent laparatomy confirmed this diagnosis and a palliative cholecyst-gastrostomy was performed.

CASE 17.—N.J. was a woman aged 52.

*History*.—She was admitted complaining of severe attacks of upper abdominal pain and vomiting over a period of 15 months. Three days before admission she had complained of a further attack of severe upper abdominal pain during which she had become jaundiced. No physical signs were present other than the jaundice and a palpable liver two fingerbreadths below the costal margin. Biochemical investigations confirmed the diagnosis of obstructive jaundice, the serum bilirubin being 3·4 mg.%, and the alkaline phosphatase 60 units. Liver biopsy showed numerous bile thrombi and proliferating bile ducts in the portal tracts together with inflammatory cells and some increase in fibrous tissue.

*Transhepatic Cholangiography*.—This was attempted on two occasions, four and five weeks after the onset of jaundice. On neither occasion could a bile passage be punctured.

*Laparotomy* subsequently revealed no evidence of extrahepatic obstruction, the common bile duct being normal in size and patent. A diagnosis of primary biliary cirrhosis was made.

## COMPLICATIONS

In patients in whom cholangiography was impossible no complications occurred. Of those in whom cholangiography was successful the condition of two patients, both suffering from carcinoma

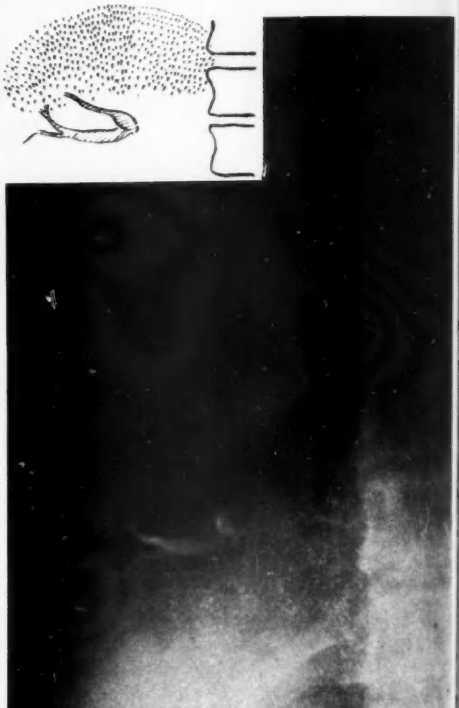

FIG. 8.—*Radiograph showing a collection of dilated ducts in the right lobe of the liver associated with extravasation of the dye into the hepatic parenchyma. No ducts were outlined in the left lobe. Diagnosis: carcinoma of the bile ducts at the porta hepatis.*

of the pancreas, gave concern. In the first of these, upper abdominal pain associated with vomiting, was present for 24 hours after the procedure and then subsided spontaneously. Subsequent laparotomy revealed no evidence of a previous biliary leakage. In the second patient, after an interval of some 60 hours, during which an apparently normal recovery took place, the patient complained of severe lower abdominal pain. On examination lower abdominal rigidity suggested a diagnosis of biliary peritonitis. Immediate laparotomy revealed the four puncture sites on the anterior surface of the liver; from one of these, a small laceration rather than a circumscribed puncture wound, bile was seen escaping. A palliative cholecyst-gastrostomy was performed and the right suprahepatic space drained. The patient made an uninterrupted recovery from this complication.

## Discussion

Two important factors must be considered in the evaluation of any diagnostic procedure. First, its safety in relation to other methods of investigation available and secondly the potential usefulness of the method in increasing the accuracy of diagnosis.

Since a procedure which is excessively dangerous cannot justifiably be used this factor requires primary consideration. In most of the reported series attention has been drawn by the authors to the main hazard of transhepatic cholangiography, namely biliary peritonitis. Indeed Richieri (1957), who found an incidence of biliary peritonitis of 30% and a mortality of 16% following this procedure, maintained that its use could not be justified. On the other hand, Meeroff (1957) reviewing more than 220 percutaneous transhepatic cholangiographic studies performed at other Argentinian clinics, records no fatality and states that biliary peritonitis ensued in only two.

Review of the literature lends support to Meeroff's view that transhepatic cholangiography is a reasonably safe technique. In addition to Richieri's 36 patients we have traced 277 cases, in 224 of which a cholangiogram was obtained (Table II). In nine of these patients biliary leakage was suspected. In two of these (Wilks, Valenzuela, and Schaposnik, 1958) the cause of this complication was ascribed to accidental puncture of the gall-bladder but in the remaining five patients leakage appears to have been from the liver itself. All except the patients reported by Leger, Zara, and Wargnier (1953) and by Nurick, Patey, and Whiteside (1953) recovered either spontaneously or after laparotomy. This procedure, therefore, carries a potential hazard which may terminate fatally. With careful technique the incidence of biliary peritonitis is of the order of 3·5%, which, however, should be weighed against the equal or greater hazard of "exploratory" laparotomy in the severely jaundiced patient.

It must be emphasized that careful control of respiration during the period when the needle is in the liver is of the utmost importance in avoiding hepatic damage and so reducing the likelihood of

Table II

RESULTS IN THE LITERATURE

| | | No. of Patients | Cholangiogram Obtained | Biliary Leak After Cholangiography | Deaths Attributed to Procedure |
|---|---|---|---|---|---|
| Huard and Do-Xuan-Hop | (1937) | 2 | 2 | 0 | 0 |
| Carter and Saypol | (1952) | 1 | 1 | 0 | 0 |
| Leger *et al.* | (1952) | 2 | 2 | 0 | 0 |
| Alvarez and Jensen | (1953) | 12 | 9 | 0 | 0 |
| Crismer | (1953) | 6 | 6 | 0 | 0 |
| Goni Moreno | (1953) | 1 | 1 | 0 | 0 |
| Leger *et al.* | (1953) | 14 | 14 | 1 | 1 |
| Michelini | (1953) | 1 | 1 | 0 | 0 |
| Nurick *et al.* | (1953) | 5 | 5 | 1 | 1 |
| Fuente *et al.* | (1954) | 4 | 4 | 0 | 0 |
| Royer *et al.* | (1954) | 6 | 6 | 0 | 0 |
| Sobredo and Garcia Siguero | (1954) | 20 | 17 | 0 | 0 |
| Kidd | (1956) | 6 | 6 | 0 | 0 |
| Mandl | (1956) | 25 | 15 | 0 | 0 |
| Remolar *et al.* | (1956) | 34 | 20 | 0 | 0 |
| Royer *et al.* | (1956) | 19 | 15 | 0 | 0 |
| Housset and Vantsis | (1957) | 9 | 9 | 0 | 0 |
| Redington *et al.* | (1957) | 14 | 13 | 2 | 0 |
| Felci | (1958) | 21 | 19 | 1 | 0 |
| Wilks *et al.* | (1958) | 41 | 38 | 2 | 0 |
| Barbier | (1959) | 4 | 4 | 0 | 0 |
| Marcasoli and Cetrá | (1959) | 1 | 1 | 0 | 0 |
| Kaplan *et al.* | (1960) | 8 | 6 | 0 | 0 |
| Present Series | (1960) | 21 | 10 | 2 | 0 |
| Total | | 277 | 224 | 9 | 2 |
| Richieri | (1957) | 36 | — | 11 | 6 |

biliary peritonitis or haemorrhage following percutaneous transhepatic cholangiography. Varela Fuentes, Bertoni, and Polero (1957) go to the length of anaesthetizing the right phrenic nerve to reduce respiratory movement of the liver before performing percutaneous transhepatic cholangiography. Housset and Vantsis (1957) advocate an intercostal approach in the mid-axillary line because they consider that this reduces the risk of these complications. However, it would seem that the chance of entering a large bile duct might be greater using an anterior approach and we therefore prefer this route as greater importance can be attached to a negative examination. Preliminary aspiration before the injection of the contrast medium diminishes the degree of distension of the biliary passages and may thus help to prevent leakage of bile. Percutaneous transhepatic cholangiography should be confined to patients who have been admitted to the ward. Moreover, the examination should only be made in patients in whom operation has been considered and can be undertaken if necessary without delay. Bile leakage is much commoner in patients with extrahepatic biliary obstruction who would in any case presumably require laparotomy.

From Table II it will be observed that this procedure was of positive value in the diagnosis of the cause of jaundice in 80% of patients. However, in our series the biliary tree was successfully injected in only 11 patients out of 21. This discrepancy between many previous series and our own is probably due to the fact that we investigated all patients suffering from jaundice with obstructive features by this method. Many of these patients were eventually found to be suffering from intrahepatic biliary obstruction without dilatation of the bile passages. The normal biliary tree is almost impossible to find by needling the liver and hence negative results would be expected in this group. Nurick *et al.* (1953) and Housset and Vantsis (1957) emphasize that the technique is impracticable in the absence of extrahepatic biliary obstruction. However, in the light of our experience, a negative examination would appear to be of as much diagnostic significance as a successful one. The biliary passages were entered and cholangiography was performed successfully in each of the patients subsequently found to be suffering from extrahepatic obstruction, whereas in none of those later found to have intrahepatic obstruction could bile be aspirated from the liver. We therefore believe that, if jaundice has been present for at least a month, failure to penetrate a bile passage after adequate needling of the liver virtually excludes extrahepatic biliary obstruction. The technique is of special value in the diagnosis of primary biliary cirrhosis which hitherto could only be distinguished from extrahepatic biliary obstruction with certainty by laparotomy and operative cholangiography. Percutaneous transhepatic cholangiography may enable operation to be avoided in these patients.

Dilatation of the biliary tree in extrahepatic biliary obstruction takes time to occur and we would agree with Remolar *et al.* (1956) that enlargement of the biliary tree is dependent more upon the duration than on the severity of biliary obstruction, hence the proviso that jaundice must have been present for at least one month before significance can be attached to a negative examination.

Percutaneous transhepatic cholangiography is useful in determining the site and cause of extrahepatic obstruction before operation, and in this respect the value of serial films in the diagnosis of biliary calculi must be stressed. The absence of any characteristic deformity of the lower end of the common duct of the rat tail variety, as produced by intrinsic neoplasms elsewhere in the alimentary tract, was rather surprising. This, however, did not detract from the practical value of the method in the diagnosis of carcinoma of the pancreas as a cause of obstructive jaundice. Unfortunately, as might have been expected, chclangiography has not helped to establish the resectability of neoplastic lesions involving the biliary passages.

## Summary

Percutaneous transhepatic cholangiography has been attempted in 21 patients suffering from obstructive jaundice of uncertain origin and the results correlated with the findings at subsequent laparotomy.

Cholangiograms were obtained in each of 11 patients later found to be suffering from extrahepatic obstruction and enabled the correct diagnosis to be made in 10 of these. In contrast, the bile passages could not be entered in any of the remaining 10 patients, each of whom was subsequently discovered to have intrahepatic biliary obstruction, nor was transhepatic cholangiography successful in one additional patient suffering from abdominal pain without jaundice following cholecystectomy.

In addition to its use in indicating the site and nature of extrahepatic obstructive lesions of the bile passages, the technique appears to offer a reliable means of differentiating between intra- and extrahepatic obstruction and is of value in the diagnosis of primary biliary cirrhosis.

One patient required laparotomy for biliary leakage from the puncture wound in the liver. Review of the literature indicates that the incidence of this complication is not greater than 5%.

We wish to express our thanks to the consultant physicians and surgeons of the General Infirmary at Leeds and St. James's Hospital who have kindly referred their patients to us. We are also indebted to Professor A. S. Johnstone for facilities which his department offered and to Dr. M. Tomlinson for his cooperation. We also wish to thank Mr. A. L. Pegg for the illustrations.

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# RADIOLOGICAL INVESTIGATION OF THE SMALL INTESTINE BY SMALL BOWEL ENEMA TECHNIQUE

BY

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This paper records some experience with the Scott Harden technique of small intestinal intubation for performing small bowel enemas. It is particularly recommended for searching for obstructive or infiltrative lesions of the small intestine.

A completely satisfactory demonstration of the entire small bowel by the usual barium follow-through series, or one of its many modifications, is often not attained in the normal subject, and difficulties are intensified in the presence of pathology. Individual loops of bowel may fill and empty rapidly, and, however short the intervals between examinations, these loops may not be shown effectively. Gross delay in the onward passage of barium may frustrate the efforts of the radiologist to show the exact site and probable nature of an obstructing lesion, or several intestinal loops may overlap and so obscure a lesion; this is particularly true of ileal loops lying in the pelvis. Since the radiologist is unable to affect the degree of filling attained in the region under immediate scrutiny, the significance of local constrictions or dilatations observed at any one examination in the series is obscure and it may not be possible to detect the changes later. Local destructive processes in the mucous membrane may be quite unrecognizable.

Dissatisfaction with the barium follow-through examination led Schatzki (1943) to adopt the small bowel enema technique of duodenal intubation, using a small rubber tube and controlled filling of the small intestine, that had been recommended earlier by Pesquera (1929). The disadvantages of this method are the uncertain delay during which the tube is awaiting its passage from the stomach into the duodenum and the high failure rate because the tube cannot be passed in reasonable time. Immediate transgastric intubation with a flexible polythene tube does not impose delay and the success rate is much higher. The technique that we have used is essentially that described by Scott Harden (1960) with minor modifications, though some early cases were examined by a single tube method.

## Description of the Method

The equipment required consists of a flexible, but semi-rigid, polythene tube, 4 mm. inside diameter (5·8 mm. outside diameter) about 1 metre long, through which a second polythene tube of 1·5 mm. inside diameter, (2·7 mm. outside diameter), about 1½ metres long, can slide easily. The distal end of each tube has a small brass ring or ferrule bonded to it so that its position can be identified radiologically. We have found that a short, tightly fitting 3- or 4-in. length of flexible polythene tube sheathed over the distal end of the outer semi-rigid tube so that it projects 2 or 3 in. beyond the tip is an advantage. The tubing is sterilized by boiling and care is taken to avoid coiling or pinching the tubes in removing them from the sterilizer. A connexion is arranged with the proximal end of the inner tube so that a suspension of "micropaque", 1 : 1 part of tap water, can be injected through it from a 50 ml. syringe.

The patient is prepared as for a barium meal examination. The object of the examination and the method are clearly explained, Nearly all patients have had a barium meal beforehand and abnormalities of the stomach and duodenal cap should be excluded before this technique is employed. The patient is then given a tablet of amethocaine to suck and the fauces are lightly sprayed with 2% xylocaine.

The tubing has been carefully examined beforehand for patency and free movement of the inner on the outer is assured. The inner tube is passed down the outer until its distal end is just short of that of the outer. An assistant holds the tubing while the radiologist passes the distal end gently through the patient's mouth over the epiglottis into the hypopharynx. The tube should progress easily with gentle pressure once the cricopharyngeus has been passed. Progress is continued until a sense of elastic resistance is felt, due to the tube impacting against the greater curve of the stomach. The tube is then withdrawn slightly and the patient is placed supine on the *x*-ray couch. We use a Marconi type 5-in. image amplifier for the examination, and take under and over

couch large films as required. (The actual screening factors used are 90-95 kV. with 0·3 mA.) When radiological examination has identified the position of the lower ends of the tubes, then the inner tube is carefully advanced through the outer until it engages the pylorus and is slipped through it as far as possible. Coiling of the inner tube within the stomach can often be avoided by rotating the patient to the right and by carefully advancing the outer tube over the inner immediately the latter shows any tendency to turn upwards. In a very few cases the duodenum cannot be intubated in spite of every effort, usually in grossly distorted stomachs with a severe cup and spill shape. As with all practical procedures increased experience brings increased facility and fewer failures. In the 21 months we have been using the technique we have attempted 73 examinations with four complete failures, one more patient refused all co-operation before trying, and in one more intubation was effected but the examination was not entirely satisfactory. The 67 patients in whom the examination was satisfactory give a success rate of, at worst, 90%, and this may well be improved upon.

When the tip of the inner tube has been introduced into the duodenum a little of the barium suspension is steadily injected under radiological control. Back flow into the stomach does not normally occur even if the tip is only in the duodenal cap. An early film is taken to show the duodenal loop and the uppermost loops of jejunum filled. Successive injections of barium suspension and tap water are made as required and the progress of the contrast medium observed, controlled filling of the intestine is attainable, and in the normal subject the caecum is reached in 15 to 20 minutes. In the abnormal case irregularities in the lumen can be examined continuously with different degrees of distension and the area can be re-examined by washing it through with water and refilling with barium.

Delay in forward flow indicates the presence of an obstructive lesion ahead and discretion must be used in avoiding proximal overfilling; nevertheless, with patience it is nearly always possible to identify the exact site of any kinking or narrowing of the lumen in a way that is rarely possible during a follow-through examination. In infiltrative lesions, such as Crohn's disease, it is possible to form a much more accurate impression of the extent of involvement as the rigidity of the unconstricted bowel can be assessed because its tubular stiffening can be recognized since filling can be made complete. Also local areas of narrowing can be recognized and their existence confirmed.

### Illustrative Cases

Figs. 1 and 2 show the appearance of the small bowel in a normal subject, as demonstrated by this method.

Case 1.—A woman aged 29 years gave a history of 11 years' diarrhoea, the bowels opening seven to 20 times daily, and periodic pain in the right iliac fossa. The onset of symptoms followed appendicectomy for pain in the right iliac fossa. Her stools were watery, green at times, and less often had blood in them. On examination a small mass was felt in the right iliac fossa.

Fig. 1.—*Normal appearances of jejunum and upper ileum with small bowel enema technique. The position of the lower end of the inner tube is arrowed, the lower end of the outer is at the cardia.*

Fig. 2.—*The whole of the small bowel, except the duodenal loop, is shown. The proximal colon is filled. The lower end of the inner tube is in the duodenal cap; there is some back leak into the stomach.*

FIG. 3.—*Film showing extensive Crohn's disease in the lower ileum, caecum, hepatic flexure, and proximal transverse colon.*

A small bowel enema showed a constrictive lesion in the lower ileum, several inches long, and shorter lesions in the caecum, hepatic flexure, and transverse colon (Fig. 3).

Operation by Mr. J. W. P. Gummer confirmed these findings and he removed 2 ft. of distal ileum and the right half of the colon. Histology showed typical Crohn's disease.

CASE 2.—A woman aged 23 years gave a history of continuous bowel irregularity and diarrhoea since the age of 9 months. For seven years she had had bouts of colicky abdominal pain. At the age of 14 radiographs had shown "distended gut". Recently, symptoms had become more severe and she was incontinent on account of the diarrhoea. Her weight was under 5 stones. Clinical examination revealed abdominal distension but no mass. She had a hypokalaemia (2·8 mEq./l.). A barium meal examination, performed at another hospital six months before her admission, was reported to show "atony of the terminal ileum". Numerous calcified glands were shown in the right iliac fossa.

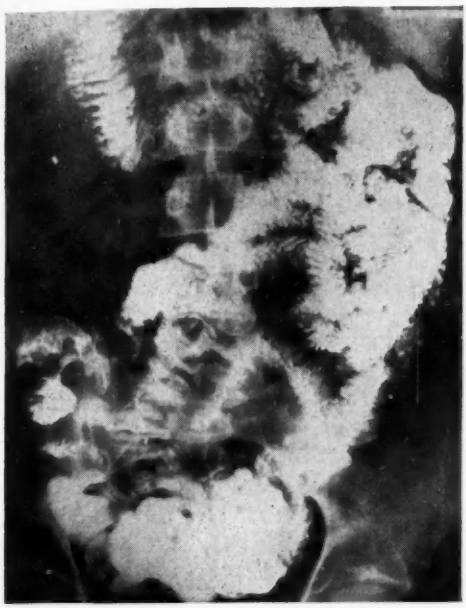
A small bowel enema (Fig. 4) showed gross distension of the terminal loop of ileum with lesser distension proximal to this. There was gross constriction of the whole of the caecum and ascending colon. The constriction terminated abruptly at the ileo-caecal valve.

Laparotomy by Mr. Gummer showed a dense fibrous mass involving the whole of the caecum and ascending colon with gross proximal distension of the ileum. A right psoas abscess was present. (There was no radiological evidence of lumbar or dorsal spine disease). Many calcified and partially calcified glands were present. The distal ileum and proximal colon were resected with great difficulty, and the descending duodenum was unavoidably opened in separating the ascending colon from it. Unfortunately, the patient died eight days later.

Necropsy confirmed the absence of any focus of disease in the spine and the psoas abscess was due to direct extension from the caecal lesion. Histology of the resected specimen showed dense fibrotic changes but no evidence of any active tuberculous lesion; granulomatous and partially calcified tuberculous disease was present in the lymph glands.

CASE 3.—A man aged 25 years gave a history of abdominal pains and diarrhoea which began six years before while he was at sea. Other members of the crew had had similar trouble at the time but their symptoms cleared up and his did not. The attacks became more frequent with the passage of time though his general health was maintained. Clinical examination showed no

FIG. 4.—*Late film showing a very dilated lowermost loop of ileum. The caecum is grossly contracted and almost entirely obscured by the large calcified glandular mass in the right iliac fossa. Fibrous contracture of caecum and ascending colon is probably due to old tuberculous disease.*



FIGS. 5 AND 6.—*Film (single tube method) showing multiple strictures in lower ileum. Histologically, necrotizing ileitis or ? Crohn's disease.*
*Fig. 5 shows the normality of the upper small bowel, and Fig. 6 five or six of the strictures.*

abnormality except for tenderness in the right iliac fossa. Repeated barium meals had shown some duodenal cap deformity. A small bowel enema (Figs. 5 and 6) showed numerous very localized constrictions in the lower ileum with intervening normal bowel. The mucosal pattern was locally destroyed. Laparotomy by Mr. Gummer showed numerous areas of stricture in the lower ileum associated with regional glandular enlargement. One of the areas was excised and histology revealed simple mucosal ulceration with necrotic areas and granulations. Dr. R. Drury reported that the appearances, though not typical, could be due to Crohn's disease. Ultimately, 4 ft. of ileum had to be resected and a right hemicolectomy be performed at a subsequent operation after a spontaneous perforation at one of the sites of constriction.

### APPLICATIONS OF THE METHOD

Success in this investigation depends on full cooperation on the part of the patient, who must be sufficiently ambulant to be able to submit to a somewhat rigorous examination. Many will have had one or several barium meal examinations and we like to have the results of these available. Abnormalities in the stomach and duodenal cap must have been excluded and films showing the outline of the stomach help in indicating the probable ease or difficulty of intubation.

Since the examination is more anatomical than physiological in character we prefer not to employ it as a primary examination in patients presenting with steatorrhoea, though we do not hesitate to use it secondarily in such patients. In spite of what has just been said, characteristic steatorrhoea-type appearances are produced when the method is applied to patients with an idiopathic or pancreatic steatorrhoea.

The method is very valuable in patients presenting with abdominal pain and diarrhoea in whom an obstructive or constrictive lesion of the small bowel is likely to be found. In patients who are known to have Crohn's disease and who have had one or more operations, sometimes of unknown nature, it is most helpful in giving the surgeon as accurate an impression as possible of the state of affairs he may have to face before he undertakes a difficult laparotomy. The presence of "blind loops" may be more than suspected. In investigating the small bowel for the source of occult bleeding it is, in our

opinion, the most effective radiological method.

In conclusion, we recommend this investigation when it can be used with care and discretion in the search for obstructive or infiltrative lesions of the small bowel or where occult bleeding is likely to be coming from a lesion below the duodenal cap. We would stress that it is not to be undertaken as a routine but its application is most advantageous in the circumstances indicated.

We are obliged to our clinical colleagues, especially Dr. F. Avery Jones and Mr. J. W. P. Gummer, for access to their findings and to Dr. R. Drury for his pathological reports on the cases quoted.

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# GASTROENTEROLOGICAL SOCIETY OF AUSTRALIA

The second annual general meeting was held at the Royal Melbourne Hospital on May 24, 1960.

*Office Bearers:*

| | |
|---|---|
| President | Sir William Morrow |
| Vice-President | Dr. W. E. King |
| Hon. Secretary | Dr. S. J. M. Goulston |
| Hon. Treasurer | Dr. A. Kerr Grant |

Other members of Council:
Dr. W. Irwin
Dr. R. Andrew
Dr. R. A. Joske

Honorary membership was conferred upon:
Dr. F. Avery Jones, of Great Britain
Dr. Hugh Butt, of U.S.A.
Dr. N. Henning, of Germany
in recognition of their outstanding contribution to gastroenterology.

After the business meeting, a scientific meeting was held. Summaries of the papers are as follows:—

R. A. JOSKE described the acute cholestatic syndrome in a summary of 13 patients with the acute idiopathic cholestatic syndrome, stressing the diagnosis, pathology, and prognosis of this disease and comparing and contrasting it with the acute cholestatic syndromes due to drugs such as "largactil" and "marsalid".

W. E. KING and S. F. PHILLIPS discussed the treatment of Wilson's disease with penicillamine based on a patient presenting in August, 1956, with a history of three months' anorexia, nausea, and dark urine without manifest jaundice. She had hepatosplenomegaly and supported by liver function tests was diagnosed as viral hepatitis. Over the following three months she improved symptomatically, the liver size decreased although the spleen remained palpable. She suffered amenorrhoea and was thought at this stage to be a case of mild persistent hepatitis.

She returned in September, 1959, with five months' history of personality variation, dysarthia and hypersalivation. Kaiser-Fleischer rings were noted in the corneae and investigation proved her to be a case of hepatolenticular degeneration. Liver function tests, still abnormal, were similar to those of 1956.

She has had treatment with the British antilewisite ("dimercaprol") and penicillamine (dimethyl cysteine) both of which markedly increase her urinary copper output. Penicillamine is preferred for long-term therapy because of its low toxicity and oral administration.

Her urinary copper output varies with the dose of penicillamine. She also has potassium sulphide by mouth to lower absorption of copper from the gut. With these measures a negative copper balance over a long period has been achieved.

Her progress has not been very encouraging. At the best they claimed to have halted what was a quite rapid deterioration. In no way has she improved on this therapy. However, it is known that treatment must be continued for many months before failure is admitted. During all this period seemingly adequate "decoppering" is being achieved.

They stressed that the important point of this case is that persistent hepatitis should not be accepted in a case of juvenile cirrhosis without first excluding Wilson's disease. The diagnosis should be possible clinically and by the use of fairly simple biochemical estimations. If this patient had been treated three years earlier she might now have had no neurological deficit. The second point is that the establishment of a negative copper balance is not the complete answer in therapy, and may in fact indicate that copper toxicity is not the prime factor in the pathogenesis of this condition.

A. P. SKYRING reported four patients with rare heritable diseases who had bled from the gastrointestinal tract as a result of local manifestations of generalized disease. In each case the disease could be diagnosed by examination of the skin. The four conditions were (1) pseudoxanthoma elasticum, (2) neurofibromatosis, (3) Peutz-Jaeger syndrome, and (4) primary amyloidosis.

I. MACKAY discussed the value of the secretin test and surgical pancreatic biopsy in the diagnosis of pancreatic disease, stating that in some cases of pancreatitis, elevated serum and urinary enzyme levels cannot be demonstrated and other evidence of pancreatic dysfunction must be sought. The secretin test and operative pancreatic biopsy were assessed from this viewpoint. The response to the secretin tests in 64 patients was graded as "normal", "equivocal", "abnormal", and "grossly abnormal". In 25 patients with relapsing pancreatitis, results of secretin tests were fairly evenly distributed in these four groups. Six patients with dyspepsia and atropic gastritis had abnormal tests.

The biopsy appearances in 21 cases of relapsing pancreatitis included normal tissue in seven cases, mixed inflammation and fibrosis in three cases, mild to moderate fibrosis in four cases, and dense fibrosis in seven cases. These findings run parallel with results of the secretin test in relapsing pancreatitis. Biopsy established the diagnosis of pancreatic carcinoma in five out of nine subsequently proven cases.

He considered that the secretin test and pancreatic biopsy should be used to indicate impairment of pancreatic function rather than to establish a specific diagnosis in pancreatic disease.

N. GALLAGHER presented evidence of persistent acute infectious hepatitis being an entity. In these patients

relapses of acute viral hepatitis occurred over long periods, up to three years. Each relapse had the typical clinical and biochemical characteristics of acute hepatitis and serial aspiration liver biopsies confirmed this. All patients recovered without any disturbance of hepatic architecture.

P. PARSONS and I. LYLE discussed the blind loop syndrome in three middle-aged women, all following short-circuit operations for recurrent small bowel obstruction. Two presented with intractable diarrhoea, one with oedema. Results of metabolic and *x*-ray and haematological studies were shown. Operative correction of the blind ileal loop was carried out in all cases.

IAN WOOD praised colour photography of the stomach by the Debray and Housset "gastrophot" gastroscope. This instrument is fitted with an electronic flash of 1/500 second and excellent pictures are obtained. He showed a representative series which included the following:—

(1) Pseudohypertrophic gastritis, the appearance being produced by inadequate inflation of the stomach: it was dispelled by full inflation and gastric biopsy showed atrophic gastritis.

(2) True giant hypertrophic gastritis which had caused gastric haemorrhage and was proven by radiographs and biopsy.

(3) Gastric atrophy which had caused pernicious anaemia and had not regenerated with intensive B12 therapy: the persistence of the atrophy was confirmed by serial gastric biopsies.

(4) Innocent ulcer of the pre-antral region in a pensioner aged 70 not revealed by *x*-ray examination.

(5) Cancer of the antrum, revealed by radiographs and proven at operation.

(6) Anastomotic ulcer with haemorrhage following gastroenterostomy for duodenal ulcer with obstruction: an *x*-ray examination had revealed no ulcer.

(7) "Zonal gastritis" in the region of the stoma following gastroileostomy performed in error for duodenal ulcer and had caused pain, diarrhoea, and severe cachexia. Radiographs had confirmed the error and biopsy showed severe gastritis.

T. KIRKLAND discussed black liver jaundice in a family.

Among six siblings two males have had recurrent jaundice, their liver cells showing a type of pigmentation described in the Dubin-Johnson syndrome.

There appeared to be no significant icterus in other members of the family. Serum bilirubin was measured in the parents and unaffected siblings; it was raised in a third brother who has had no symptoms. In the third generation seven children have not been jaundiced, but their sera have not been examined. Both brothers with symptoms have had abdominal pain, in one case severe. The mechanism of the pain has not yet been explained.

R. ANDREW presented a clinical study of oesophageal hiatus hernia based on his personal experience of 91 cases. Almost all experienced chest or abdominal pain or discomfort, rarely severe and often waking the patient at night. The association of peptic ulcer was high. Oesophagitis was a common feature. About one quarter gave some history of vomiting blood but this was rarely of any severity. Eighty-three patients were managed medically, half doing well and a quarter poorly. Only eight were submitted to surgical repair of the hernia and of these four suffered a recurrence and only two had a good result.

At the annual meeting of the Royal Australasian College of Physicians held concurrently Professor C. R. B. Blackburn presented a case report of a patient who died of liver disease and renal failure. She had cirrhosis of the liver, had a splenorenal anatomosis performed some five years ago, developed high output state and arterial oxygen unsaturation. Full studies revealed the presence of venoarterial shunt of some magnitude and she ultimately died. At necropsy the patency of the anastomosis was demonstrated, and by plastic injection techniques clear-cut pulmonary-arterial venous shunting was demonstrated.

D. W. PIPER gave a paper on the effect of anticholinergic drugs on gastric secretion. A study was made of the effect of anticholinergic drugs on the various components of gastric secretion. With increasing dose, the acid could be inhibited by about 80%. Though pepsin secretion was diminished the output of pepsin was less inhibited than the volume of secretion with a subsequent rise in pepsin concentration. As regards the electrolytes, with increasing anticholinergic suppression of secretion the output of Na and K showed a slight fall, the concentration of Na rose, and the concentration of K showed a slight fall.

When a series of drugs were compared as regards their effect on saliva and gastric secretion, he found that those that are the most powerful inhibitors of gastric secretion also cause a fall in saliva flow. Two new drugs were studied, oxyphencyclimine hydrochloride and propionyl atropine methyl nitrate. The former was found to have a longer duration of action than the commonly used preparations; propionyl atropine methyl nitrate was found to have virtually no effect on gastric secretion.

A study on post-gastrectomy malabsorption was presented by KINSELLA, W. B. HENNESSY, and E. P. GEORGE.

Several nutritional problems after gastrectomy are rare, but on the other hand, weight loss of varying degree is common. The reasons for this are probably multiple and include (1) reduced food intake, (2) improper admixture of food with bile and pancreatic secretion, especially after a Billroth II gastrectomy, and (3) too rapid passage of food through the small intestine.

Additional factors also may be important. For example, bacterial flora operating under conditions suitable for their growth can cause gross malabsorption after gastrectomy. Normally the small intestine is sterile and this appears to be due to an antibacterial mechanism which is independent of the secretions of the stomach (Cregan and Hayward, 1953). However in some patients following total or subtotal gastrectomy this mechanism

breaks down and bacterial contamination of the upper small bowel occurs.

Three cases were presented to show that stasis in the afferent limb of a Billroth II anastomosis is a possible cause of bacterial contamination of the upper jejunum. Two of these patients were treated with broad-spectrum antibiotics and responded favourably. Subsequently, bacteriological studies were carried out at operation. It has been suggested (Wirts *et al.*, 1959; Kinsella and Hennessy, 1960) that such cases are examples of the blind loop syndrome. Other possible causes of stasis include obstruction of the efferent loop of a Billroth II anastomosis and vagotomy. Two additional cases were shown to illustrate this complication.

They further stated that post-gastrectomy steatorrhoea may exist without obvious afferent or efferent loop obstruction. Moreover, although more frequent following the Billroth II operation, steatorrhoea may occur after a Billroth I gastrectomy. With the aid of $^{131}$ labelled triolein, the steatorrhoea in the majority of these patients is found to diminish following the use of chemotherapy and antibiotics. It is assumed that the antibacterial mechanism in the small intestine has broken down in such cases but the real reason for this is uncertain.

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# THE SEPTEMBER (1960) ISSUE

The September (1960) issue contains the following papers:—

Post-gastrectomy Syndromes: A Review. C. F. W. ILLINGWORTH.

The Use of Cholecystokinin to Test Gall Bladder Function in Man. P. BURTON, A. A. HARPER, HENRY T. HOWAT, J. E. SCOTT, and H. VARLEY.

Gastric Cytodiagnosis: A Review and Appraisal. D. D. GIBBS.

An Assessment of Prednisone, Salazopyrin, and Topical Hydrocortisone Hemisuccinate Used as Out-patient Treatment for Ulcerative Colitis. J. E. LENNARD-JONES, A. J. LONGMORE, A. C. NEWELL, C. W. E. WILSON, and F. AVERY JONES.

A Clinical and Statistical Study of the Effect of Gastrojejunostomy on Human Gastric Secretion. H. I. TANKEL, I. E. GILLESPIE, D. H. CLARK, A. W. KAY, and J. MCARTHUR.

A Comparison Between the Effects of Hexamethonium and Atropine in Combination and of Vagotomy with Gastrojejunostomy on Human Gastric Secretion. J. MCARTHUR, H. I. TANKEL, and A. W. KAY.

Massive Resection of the Small Intestine after Occlusion of the Superior Mesenteric Artery. R. J. HARRISON and C. C. BOOTH.

Factors Influencing the Growth of *Staphylococcus aureus* in the Stomach after Gastric Operations. F. G. SMIDDY and D. PRATT.

Gastric Activity in the South African European and Bantu. I. MACDONALD.

Benign Duodeno-colonic Fistula. G. N. CHANDLER and A. J. LONGMORE.

Surgery in Bleeding Peptic Ulcers. J. N. WARD-MCQUAID, J. C. PEASE, A. MCEWEN SMITH, and R. J. TWORT.

*New Methods for Diagnosis and Research*

Wireless Telemetering from the Digestive Tract. A. M. CONNELL and E. N. ROWLANDS.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

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